IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

IN RE:)
NEURONTIN MARKETING, SALES PRACTICES) CA No. 04-10981-PBS
AND PRODUCTS LIABILITY LITIGATION) Pages 1 - 106

DAUBERT HEARING - DAY ONE

BEFORE THE HONORABLE PATTI B. SARIS
UNITED STATES DISTRICT JUDGE
and
JUSTICE MARCY S. FRIEDMAN
NEW YORK SUPREME COURT

United States District Court
1 Courthouse Way, Courtroom 19
Boston, Massachusetts
June 19, 2008, 2:10 p.m.

LEE A. MARZILLI
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I N D E X

P R O C E E D I N G S

THE CLERK: In Re: Neurontin Marketing and Sales Practices and Product Liability Litigation, Civil Action No. 04-10981, will now be heard before this Court. Will counsel please identify themselves for the record.

MR. FINKELSTEIN: Andrew Finkelstein, Finkelstein & Partners, on behalf of the product liability plaintiffs. Good afternoon.

MR. FROMSON: Good afternoon, your Honors. Kenneth Fromson, Finkelstein & Partners, on behalf of the products liabilities plaintiffs. Along with me is Keith Altman. He's an employee of the law firm and not an attorney.

MR. LONDON: Good afternoon. Jack London. I'm on the plaintiffs' Products Liability Steering Committee, and I'm here on behalf of the plaintiffs, and with me is Mr. Khin Soe.

MR. ROUHANDEH: Good afternoon. Jim Rouhandeh from Davis, Polk & Wardwell for the defendants.

MR. HOOPER: Your honors, Jim Hooper from Wheeler Trigg Kennedy for the defendants.

JUDGE SARIS: It's such a large courtroom and there are lots of people. Would anyone want to move in here, no vote but you get to see better? Anyone who wants to is certainly welcome to. And if you have to leave, I won't view it as insulting if you slip out, so you're not stuck. So if

people want to, you're certainly welcome to, especially since we've moved the monitor. Is there a reason we have moved that? So there is one behind, so you all can see? Good, all right. I'm sorry to interrupt you.

MR. SAYLER: Good afternoon, your Honor. Scott Sayler, Shook Hardy & Bacon, representing defendants.

MR. CHAFFIN: Good afternoon, your Honor. David Chaffin, Hare & Chaffin, for the defendants.

MR. BARNES: Good afternoon, your Honors. Richard Barnes on behalf of the defendants from Goodell DeVries Leech & Dann in Baltimore.

MS. HELLWIG: Good afternoon, Diane Hellwig, Wheeler Trigg Kennedy, in behalf of defendants.

MS. STEVENSON: Good afternoon. Jennifer Stevenson from Shook, Hardy & Bacon on behalf of defendants.

MS. KAUFMAN: Beth Kaufman, Shoeman Upkike & Kaufman, for the defendants.

MS. McGRODER: Lori McGroder, Shook, Hardy & Bacon, on behalf of defendants.

JUDGE SARIS: Anyone else? All right. Well, this is a joint proceeding, which is highly unusual, between the Federal Court and the State Court of New York, and so we will be presiding jointly, and we've just had lunch. And I wanted to at least go through our understanding. A Frye hearing under New York law is actually substantially different than a

Daubert hearing under federal law, but my understanding is, whatever you call it, the Rules of Evidence will not apply, all right? So we were trying to think, "Well, what happens if someone objects" and I say "Sustained" and she says "Overruled"? So that's a little awkward. So we're going to just try -- we're learning working together as we go, but I'm assuming, because the Rules of Evidence don't apply, that there will be a minimum of objections. You very carefully have scripted it. This is an extremely important proceeding having to do with Neurontin, gabapentin.

You're both going to do opening statements, is that correct, for about a half an hour apiece, was that how we were going to do it, to lay out what you were intending to prove and why this is significant under both federal and state law? And then, ideally speaking, what we're going to do is go tomorrow morning rather than tomorrow afternoon. The trial that I had was continued, so I actually have tomorrow morning open as a block, and so some of you maybe can get out of town early tomorrow.

So why don't we get going. Is there anything else housekeepingwise?

MR. FINKELSTEIN: Quite simply, your Honor, based upon the joint stipulation that was put forward and the order electronically that was filed by the Court, the opening statements were to be fifteen minutes apiece, given the time

constraints.

JUDGE SARIS: Fine. Who's first? It's technically your motion, right, to strike?

MR. SAYLER: Yes, your Honor.

JUDGE SARIS: And nice and loudly, and there's a mike there, just because a lot of people want to hear what you have to say.

MR. SAYLER: Thank you very much. May it please both Courts, in every case where plaintiffs are contending that Neurontin caused a suicidal event, plaintiffs bear the burden of establishing that they have admissible expert testimony that Neurontin can and has caused suicidal events.

Plaintiffs have designated three experts who offer general causation opinions: They are Drs. Stefan Kruszewski, Cheryl Blume, and Michael Trimble. Defendants' position is that plaintiffs have failed their burden of establishing that these experts' general causation opinions meet the admissibility requirements under the Federal Rules of Evidence, Daubert, and Frye.

After hundreds of pages of reports, testimony, and briefing by plaintiffs and their experts, the essential facts upon which defendants base their Daubert and Frye motions remain unchanged. First, the placebo-controlled clinical trial data specific to Neurontin fails to establish a statistically significant association between Neurontin and

suicidal behavior and thinking, and in just a moment I will get into the data on that subject that has been part of the FDA's analysis.

Second, no epidemiologic study or testing establishes that Neurontin is associated with or causes suicide-related events, and in just a minute I will get into the one epidemiologic study the plaintiffs' experts relied upon in this case.

Third, plaintiffs have not disputed that there is no peer-reviewed literature of any kind that opines or concludes that Neurontin can cause a suicidal event. There's no published case report that opines or concludes that Neurontin was the cause of a suicidal event. No scientist or medical doctor, except for plaintiffs' three litigation experts, has ever formally stated or concluded in a peer-reviewed context that Neurontin can cause suicide-related events. Similarly, no scientist or medical doctor, other than plaintiffs' three general causation experts, has ever formally stated or concluded that Neurontin has a mechanism of action that leads to suicide-related events; and no scientific or medical body has ever concluded that Neurontin causes suicide-related events.

Fourth, and perhaps most significant, the plaintiffs' general causation experts have made no effort to conduct any epidemiologic testing to support their general

causation opinions. The plaintiffs did designate another expert, a Dr. McFarland, who did conduct epidemiologic testing relating to Neurontin and suicidality, but his testing did not show what the plaintiffs are contending, and therefore they haven't designated him as a general causation expert.

So what we have, we would submit, is that on the basis of an untested and unproven hypothesis, the plaintiffs are seeking to have you allow them to ask juries across the country and across the state of New York to conclude what no medical or scientific community has concluded, that Neurontin can cause suicide-related events.

Is your screen working, your Honor?

JUDGE SARIS: Sure.

MR. SAYLER: Let me turn to the Daubert and Frye standards governing the admissibility of plaintiffs' general causation expert testimony, and I won't spend much time on this. As the Court is aware, Daubert and Federal Rule of Evidence 702 require this Federal Court to act as the gatekeeper and exclude expert testimony where the party offering the testimony has failed to meet its burden establishing, among other things, that the expert testimony is relevant and reliable. The relevancy, or fit, requirement refers to the necessity of a connection between the expert's testimony and the facts of the case. These are the --

JUDGE SARIS: You know, I actually don't think it's a good use of your time to go through the general standards.

MR. SAYLER: Okay, I won't. I've got the reliability standards up here, I've indicated the Frye general acceptance test, and so I will move on to an application of these standards. With these in mind, let me spend a minute talking about the reliable and accepted scientific method for assessing general causation.

The Federal Judicial Center's reference manual on scientific evidence provides guidance on the proper methodology to be followed. What the reference manual provides is that in assessing general causation, the first question scientists must ask is whether the results of an epidemiologic study establish a statistically significant association between the drug and the events at issue. If, and only if, a statistically significant association is established do scientists then move on to assessing whether there's a causal relationship, applying the Bradford Hill criteria.

The FDA's position on this is similar. In a letter written on April 1, 2008, the FDA, speaking specifically to antiepileptic drugs and suicidality analysis, stated that it doesn't believe spontaneous post-marketing reports can be interpreted appropriately in this situation. "Patients taking these drugs have a high background rate of suicidal

thoughts and behaviors. It's not possible to tell from adverse event reports whether the drugs caused them. In the agency's view, the only way to establish whether or not the drugs are responsible for suicidality is to analyze controlled clinical trial data."

And I would submit that this method of assessing general causation is exactly what the court in the Lynch case, a First Circuit decision we discussed, have done, and what the New York court in the Bextra/Celebrex coordinated products liability proceedings did, as explained in Justice Kornreich's opinion issued last January.

Okay, with this standard in mind, I will preview the Neurontin controlled clinical and epidemiologic data that the plaintiffs' experts relied upon. In March of 2005, the FDA asked the manufacturers of eleven different antiepileptic drugs, or AEDs, to analyze their placebo-controlled clinical trial data using detailed protocols spelled out by the FDA. Through blinded reviews, all cases were reviewed to determine whether they belonged in one of several categories relating to suicidal behavior or thinking. After this review, the blinds were broken and the cases were categorized.

In June of 2006, Pfizer submitted its data on Neurontin, and this is what its data showed. Its data showed that in 5,194 gabapentin, or Neurontin, patients, there were no completed suicides, no suicide attempts, no preparatory

acts toward imminent suicidal behavior, and two cases of suicidal ideation. In the placebo group, there was one case of suicidal ideation in a patient population that was roughly half the size. So the incident figures were .039 percent versus .037 percent. Graphically, it looks like this. It is undisputed that these figures do not establish a statistically significant association between Neurontin and suicidal thoughts or behaviors.

Pfizer submitted this data. The FDA took this data along with the submissions from the manufacturers of ten other AEDs, and it pooled the data. It pooled the data, and in an FDA alert that went out on January 31 of 2008, the FDA stated that it has analyzed the data, and in the FDA's analysis, patients receiving AEDs had approximately twice the risk of suicidal behavior or ideation, .43 percent, compared to patients receiving placebo.

Now, the FDA has since done some recalculations and reanalysis of its data where it's pulled out certain clinical trials and grouped them different ways, and it actually came out with a statistical review of the data last week that is very informative on the issue, but the numbers from the January 31 FDA alert look like this, the Neurontin numbers versus the FDA pooled data numbers.

Now, even with the new statistical analysis, there are several key take-away points that come from an

understanding of the FDA alert as well as the statistical analysis published last week. There's a critical difference between the Neurontin data and the AED pooled data. The Neurontin data do not demonstrate a statistically significant increased risk; the pooled data do.

Pooling the Neurontin data with data from different AEDs doesn't change the Neurontin data. It simply means that it's been pooled with other data. The FDA specifically emphasized that it was making no causality finding and has not made a causality finding to this date.

Finally, and perhaps most significant, the FDA alert didn't indicate which drug or drug's data was responsible for the increased risk, but we know it was not Neurontin. The FDA's statistical review clarifies that the increased risk in the pooled data is attributable to data from two drugs. Here's a chart taken from the data and the statistical review that was published last week. In the pooled data, the FDA identified 104 cases of suicidal behavior or thinking. Of those 104 cases, 27 came from a drug called lamotrigine, and 40 came from a drug called topiramate. So 67 of the 104 cases came from those two drugs. As you can see, two of the 104 cases came from gabapentin. We will demonstrate in the coming days that if you pull out the lamotrigine and topiramate data and you analyze the other data, pooled or individually, there's

absolutely nothing there, absolutely nothing there.

We would submit that the FDA's analysis represents a risk analysis of a pool of drugs being done for regulatory purpose. The FDA is not asking the question that is being asked by this Court, and that is, do plaintiffs have reliable scientific evidence on causation?

There are a number of courts, including this Court in the Sutera case, the New York court in the recent Bextra/Celebrex decision, the New York Court of Appeals in Parker V. Mobile Oil, all have concluded that regulatory risk assessments and actions shall not be used to support a finding of general causation.

Okay, I am going to very quickly go through this epidemiologic study, the McFarland study.

JUDGE SARIS: You've only got three minutes.

MR. SAYLER: I know, my time is running out, but I'm just going to summarize it by saying this is an epidemiologic study that was done looking at the suicidality in a bipolar population. The results of this study showed that both Neurontin and lithium suicide rates were well below the background rates of suicide in bipolar populations. The author went on to explain that the difference between the lithium and Neurontin rates was due to Neurontin being prescribed in pain populations and also lithium having a protective effect. But the author reached no general

causation conclusion, and if anything, this epidemiologic study supports the hypothesis that Neurontin may be protective against suicidal behavior or thinking.

Applying the data to the Daubert factors, there is no testing that supports the plaintiffs' case. There's no epidemiologic or clinical testing that supports the plaintiffs' case. Given that there is none, there can be no rate of error. There is no acceptance for the proposition that Neurontin causes suicidal behavior or thinking, and there's no peer review or publication that reaches such a conclusion. Two of the plaintiffs' experts did not even consider the issue of Neurontin and suicidality until they were hired in this litigation. The other one reached previous inconsistent conclusions. The plaintiffs are extrapolating from theories of biological plausibility to a causation determination. This is the definition of "unjustifiable extrapolation." There are obvious alternative explanations for suicidality, given the huge background rate of suicide in the populations at issue.

We would submit that plaintiffs' evidence fails to satisfy Daubert and fails to satisfy Frye.

JUDGE SARIS: All right, thank you. Do you have all these slides for us?

MR. SAYLER: I sure do.

JUDGE SARIS: Two sets, so maybe you'd put for the

record and we'll each take a set?

MR. SAYLER: Absolutely.

JUDGE SARIS: Do you have those?

MR. SAYLER: I think we can get those to you immediately, yes, your Honor.

JUDGE SARIS: So maybe Robert can mark them anyway, and then we'll each get copies?

MR. SAYLER: Yes.

JUDGE SARIS: Because otherwise your opening wouldn't make sense. Okay, great, thank you. Did you have more?

MR. SAYLER: I had a little bit more. A few minutes real quick?

JUDGE SARIS: It's been fifteen minutes. We've got to be tight. Quick, okay.

MR. SAYLER: Quickly, your Honor, the Lynch case, it's a key case. It's a case where --

JUDGE SARIS: It's the linchpin?

MR. SAYLER: Exactly, it's the linchpin. It's a case where there were no epidemiologic studies. The plaintiffs' experts offered the type of evidence that the plaintiffs' experts offer here. The First Circuit held that studies of that sort, animal and in studies of analogous chemicals, don't prove causation in human beings in the absence of confirmatory epidemiologic data. Without such a

study, there's nothing on which expert opinion may be based. The plaintiffs offered no new study. This is a pre-Daubert opinion which was actually strengthened by Daubert.

I would also recommend the Bextra/Celebrex decision that I mentioned earlier, a very similar case where the court held that even though the plaintiffs offered biological reliability hypotheses and other evidence, they didn't have the epidemiologic data; and the experts were excluded on opining that Celebrex causes cardiovascular disease at 200 milligrams.

JUSTICE FRIEDMAN: I read it this morning.

MR. SAYLER: Great, that's great. I will sit down now. We believe that the plaintiffs, they rely very heavily on biological plausibility theories and individual case reports. We will demonstrate the unreliability of the data, and also the fact that the plaintiffs, we believe, are distorting the scientific and factual record.

JUDGE SARIS: Thank you very much.

MR. SAYLER: Thank you.

JUDGE SARIS: Do you have slides as well?

MR. FINKELSTEIN: I do.

JUDGE SARIS: It might be useful. I didn't think to ask beforehand, just to make sure that those are available.

MR. FINKELSTEIN: If I may, your Honor, and,

frankly, there may be a couple of words that are slightly modified because as we're sitting here, we changed a couple words.

JUDGE SARIS: I neglected to ask, is there anyone here from the Food and Drug Administration? As everyone knows here, I sent a letter requesting. We heard back from a staff member basically asking what are the briefs that would be relevant to read, and I gave them the Pacer number, and I still don't have a response as to whether or not they're going to participate. I requested participated, as you know, from the Food and Drug Administration, and I just have not definitively heard back. They know about us. That much I can be sure of.

All right, excuse me. Go ahead.

MR. FINKELSTEIN: Good afternoon, your Honors. May it please the Court, before I even start, Judge Friedman, I just want to thank you for taking the trip up here. You've saved a lot of people a lot of time and energy all coming to New York once again, and I know the inconvenience, and thank you on behalf of all the plaintiffs.

JUSTICE FRIEDMAN: Thank you.

JUDGE SARIS: How many cases are there in New York?

MR. FINKELSTEIN: Total, I think it's in excess of 400. I don't know the exact number.

JUDGE SARIS: And in the federal level, what's left?

MR. FINKELSTEIN: The federal level, oh, 300, I think? I'm not certain.

Your Honors, FDA has confirmed the experts' opinions. The experts voiced their opinion that gabapentin increases suicidality before the FDA issued their alert. The FDA alert merely confirmed that which they already knew and opined. The methodology underlying the experts' opinion is scientifically valid. The reasoning was properly applied to the reliable scientific evidence which I will outline for you very briefly. The FDA validated the experts' opinions, and this came as no surprise to any of the experts that were put forth here.

Gabapentin is associated with suicidality. This Court, and what we submit, how does this drug when you take this drug convert somebody to become suicidal? Well, a basic understanding that gabapentin is psychoactive: You take the drug; it changes brain chemistry.

It's important on how it changes the brain chemistry. Gabapentin increases brain GABA. GABA is an inhibitory neurotransmitter. There are two types of neurotransmitters in the brain, excitatory and inhibitory. GABA is the most ubiquitous neurotransmitter. It increases GABA. I will outline momentarily how we know that, but

that's confirmed through independent studies, human studies, spectroscopies and so on. There's sufficient data that supports that. Pfizer acknowledges it.

When you have increased GABA, it decreases serotonin. This too is supported in the defendants' documents. It's supported through animal studies. It's supported through clinical trials. Reduction of serotonin has predictable effects.

Serotonin is the neurotransmitter that's excitatory as compared to the inhibitory GABA. The excitatory neurotransmitter serotonin is the most recognized neurotransmitter associated with mood and behavior. The very foundation of this drug company's sales related to Zoloft and how they go about promoting their drug is, "Let's increase serotonin. Low serotonin is bad." Well, they also manufacture a drug that reduces serotonin. The results of reducing serotonin is, it increases suicidality, as demonstrated through the FDA alert, together with all the biological foundations that support this.

The experts in this case evaluated suicidality by considering whether taking a drug, gabapentin, is associated with these various considerations. When a human being takes the drug, was there a strength of an association with suicidality? Was there consistency in the findings related to increasing GABA and reducing serotonin? Was there

specificity related to the ingestion of the drug? How about temporality? Did it happen relatively close to taking it? This is what the experts evaluated. Was there biological plausibility, a biological gradient, coherent experiments that support this, and any analogies to similar drugs? By so doing and in such an evaluation, they satisfied Daubert and they satisfied Frye because every study that they examined was generally accepted as reliable. Most of them were done by Pfizer.

Frye is satisfied because of the general acceptance test. There were no novel scientific techniques that were performed here. There's no test that's surrounded with any aura of infallibility. It's not like there was a lie detector which is subject to originally a Frye test or a Breathalyzer. There was no new minted syndromes. We're not talking about a syndrome of child abuse syndrome, which is classic Frye. So Frye was satisfied. It was satisfied because our experts applied generally acceptable methods.

The evidence available to our experts in making this evaluation were the animal data, the human data, the epidemiological data, and case reports. At this time we have submitted the supporting documentation. I'm going to walk through it, but in our motions, I don't know if formally, but formally here I'm now asking admission for purposes of this hearing all of our exhibits, which were, I know, extensive,

but it supports all of these subject areas and is central to the area, and I'm simply asking for admission formally at the hearing.

The methods that our experts followed were consistent with what the FDA tells industry. So if a pharmaceutical company suspects that a drug is causing an adverse event, they think it's doing something bad, they tell the pharmaceutical company, "This is what we want you to do"-- and it's outlined in Guidance for Industry -- "We want you to take a look at case reports, look at epidemiology, look at the pharmacology, the pharmacodynamic, pharmacokinetics, and look at other drugs in the class, synthesize all that material and then give it to us." It's outlined very clearly here.

So they synthesize -- this is what a pharmaceutical company does -- and gives it to the FDA. What does the FDA do? The FDA doesn't simply adopt what these pharmaceutical companies give them. They then go through their own analyses to make an evaluation as to whether or not that drug is causal or associated with the adverse event, in this case suicide.

So the FDA undertakes similar considerations that the experts in this case undertook. They examine strength of association. FDA examines temporal relationship, consistency across various data sets, evidence of a dose-response

effect. Is there a biological plausibility? Pfizer stands up here and says, "You shouldn't look at biological plausibility." The FDA does. It's how you look at whether a drug causes an event. The seriousness of the event: Nothing more serious than death. This case deals with suicides, death. The FDA has examined it, and they have rendered what they believe.

The plaintiffs' experts, and I'm going to run very quickly through some of the supporting materials, but all of the materials that they relied upon were generally accepted, reliably scientific.

What's the evidence that supports that gabapentin increases GABA? Well, there's a spectroscopy. A spectroscopy is similar to an MRI, but it studies brain. You take a drug, and they see, how does it change the brain chemistry? So there was a study. They took some people. They checked out their brain. They ran it through the machine. Then they gave them the drug, and they took another study six hours later. They did this in two independent, at Yale and University of Alabama. That's replicated. That's important. So this replicated spectroscopy finds that gabapentin increases brain GABA. It's not even in dispute.

Well, why is this important for purposes of the methodology that the experts followed? It's important because related to causal considerations, it shows strength

of an association. It shows consistency, temporality, a biological gradient, experiment, and coherence.

And what's interesting is, when these spectroscopies come out and Pfizer reads about them and we have access to their internal documents, their internal psychiatrist in charge of research and development reads it, and this is what he says in an e-mail: "It strikes me that increased GABA in human brains might contribute to adverse event in humans." This isn't novel, but this is what he says.

Now, we know that increased GABA decreases serotonin. How do we know that this is so? There's several supporting materials, but the Pfizer did an extensive study -- and this is dated from 1981 to 2001 -- of all their research reports regarding animal pharmacology. It was written by Charlie Taylor. He's in the courtroom here. You're going to hear from him tomorrow. This is thousands of pages long. But what does it consistently say throughout it as relates to the effect of gabapentin on serotonin? It says: Inhibition of neurotransmitter released by gabapentin. Serotonin was also reduced. Gabapentin inhibits the release of serotonin.

When doctors call up and they say, "Tell me about gabapentin," what do they say? Pfizer writes them a letter and says it reduces the release of monoamine

neurotransmitters. Monoamine neurotransmitters is serotonin.

Then what's the proof that low serotonin or you extract serotonin from the brain, that it increases suicidality? One of the Pfizer experts wrote a book. And there's a tremendous amount of literature related to this. This is one of the most secure findings in all of biological psychiatry that low serotonin increases suicidality. Well, Dr. Jacobs writes, and he admits, that "At least part of the pathology related to suicidal behavior is reduced serotonin turnover." There's nothing novel here. There are no surprises. They know about this. Their experts know about it.

Pfizer even admits the association, and I just want to take one moment as to really what we're doing here. What this Court is asked to decide is, does this drug have the general capacity to lead to suicidality? The general capacity, can it do it? We'll get to specific causation on individual cases, but what's before this Court, can it do it generally?

Well, they say it does. They say it does in their own clinical trials. They had a dechallenge, rechallenge. They gave the person the drug; they became suicidal and depressed. They took the drug away; the suicidality and depression went away. They gave it back; the suicidality

came back, depression came back. What did their investigator say? Their investigator said, "This is probably related to gabapentin therapy."

They're not the only ones. Health Canada did the same thing. Health Canada being the same as the FDA here, Health Canada says, "One suicide was found to have a positive dechallenge/rechallenge, indicating that this event was related to gabapentin." So when they stand up and say "absolutely no evidence," that's because they put their head in the sand. They just don't look at it. But it's all here, and it's in our papers.

Our experts, exquisitely qualified. You'll hear from Professor Trimble. Professor Trimble wrote the book on biological psychiatry. We're going to hear about this. He wrote the book, second edition, writing the third edition. No one more qualified. And he dedicated his career to examining what? Antiseizure drugs, effect on mood and behavior, over 200 articles written, several chapters in books, 175 peer-reviewed, and --

JUDGE SARIS: You're about fifteen minutes now, so you need to wrap it up.

MR. FINKELSTEIN: I'm wrapping up. Dr. Blume, she does the work for pharmaceutical companies, and you'll here from Dr. Kruszewski.

FDA most recently two weeks ago, they reconfirmed.

You heard about it. There's statistical review. Their conclusion, very simple: "Antiepileptic drugs are associated with increased suicidality relative to placebo. The effects are consistent among all eleven."

Their statement trying to extract out -- and we'll hear how they're trying to manipulate the data -- FDA didn't do it. They have the expert biostatisticians. They looked at it. If it wasn't across all eleven, they wouldn't say so.

Plaintiffs' experts meet Daubert. They satisfy Frye. The defendants' motion to exclude should be denied.

Thank you.

JUDGE SARIS: All right, thank you.

So, first, how did you divide up? Who's going to call the witnesses?

MR. FINKELSTEIN: We are presenting Professor Trimble. They have one hour of cross-examination. We then have a half hour of redirect. Every witness is that way. It will be Professor Trimble, then Dr. --

JUDGE SARIS: So just to make sure, everyone agrees that the various reports of the doctors are admitted with all the exhibits attached?

MR. FINKELSTEIN: Sure.

MR. SAYLER: Yes, your Honor.

JUDGE SARIS: So that way, essentially his direct

testimony is his report? Is that how we're going to --

MR. FINKELSTEIN: Sure.

JUDGE SARIS: And then you'll cross, and then you'll have some redirect. So we'll assume the direct is essentially his report. Everyone's all right with that? And I know there's some debate about Dr. Gibbons, which report, et cetera, so it will be with every doctor except Dr. Gibbons. Some of Gibbons will come in. The question is how much of it, and I'll deal with that later.

JUSTICE FRIEDMAN: Can we just confirm that there is no difference between the reports that were submitted on the Frye motions and the reports that were submitted on the Daubert motions?

MR. FINKELSTEIN: They're exactly the same. The expert reports are exactly the same.

JUSTICE FRIEDMAN: Thank you.

JUDGE SARIS: Dr. Trimble, is he the first up at bat?

MR. FINKELSTEIN: Yes.

JUDGE SARIS: Come on up, Dr. Trimble.

MICHAEL ROBERT TRIMBLE

having been first duly sworn, was examined and testified as follows:

THE WITNESS: I do prefer to stand, if that's possible, your Honors.

JUDGE SARIS: You want to stand?

THE WITNESS: If that's possible.

JUDGE SARIS: You know, in the state courts, it's actually called the "stand" because in the old state courts, you actually did stand. So if you want to go back to the original colonial courthouse technique, go ahead.

THE WITNESS: Thank you.

THE CLERK: Sir, would you please state your name and spell it for the record.

THE WITNESS: My full professional name is Professor Michael Robert Trimble, T-r-i-m-b-l-e.

JUDGE SARIS: The only concern, now that I'm thinking about it, is, the mike doesn't go up as tall as you are.

THE WITNESS: I will sit, I will sit.

JUDGE SARIS: Do you have a bad back? Is it because you have a bad back? You could just go up and down if that's an issue for, okay?

MR. HOOPER: Judge Saris, Justice Friedman, may it please the Court, for convenience, I've prepared some binders for the documents that we may ask about. I prepared one for each of you and for the reporter and the witness. Would you mind if I passed those out?

JUDGE SARIS: Perfect. If you have an extra one for the law clerks, it would be great.

MR. FINKELSTEIN: I'd love one too, if I'm allowed.

JUDGE SARIS: You want to do that now?

MR. FINKELSTEIN: Well, if he has one.

JUDGE SARIS: Oh, I thought you meant you --

CROSS-EXAMINATION BY MR. HOOPER:

Q. Professor Trimble, if you'd look at Tab A. First, we've met before, correct?

A. Correct.

Q. I took your deposition last October on October 18, correct?

A. That's correct.

Q. Nice to see you again. And if you look at the binder and Tab A in the binder, could you confirm for me that that is a copy of the expert report that you filed in this case?

A. That is correct.

Q. Professor Trimble, you have conducted no experimental research specifically related to your work in this case, correct?

A. Incorrect.

Q. Please turn to your deposition, sir. It's at the second-to-the-last tab of the binder, Page 121.

A. I have it.

Q. Thank you, sir.

MR. HOOPER: May I approach the witness, your Honor?

JUDGE SARIS: Oh, I'm sorry. Go ahead.

Q. Professor Trimble, if you would, look at Page 121. Are you there?

A. Yes.

Q. And Lines 14 to 17?

A. Yes.

Q. Let me see, if I may, if we can look at it together, "Question: Between those dates, let me ask you, have you conducted any experimental research specifically related to your work in this case?" Your answer under oath, sir, was "no," correct?

A. Correct.

Q. Professor Trimble, you've performed no biostatistical analysis of any other researcher's data in connection with your work in this specific case, correct?

A. That's correct.

Q. You've designed no tests --

JUDGE SARIS: Wait. You know, this isn't going to be like a criminal trial. All right, so did you have anything else you wanted to say?

THE WITNESS: Well, Mr. Hooper's first question is whether I'd done any work in this area in relation to this case. For the last 30 years, I've been studying this area, so a lot of the work that I brought to this case was done before I was even involved in the case. So the question was

an ambiguous one. I have done a lot of work in relationship to the central issue in this case.

Q. Sir, since you were retained in this case by Mr. Finkelstein, have you conducted any experiment in which any patients were exposed to gabapentin?

A. That's a different question. I have not.

Q. You've designed no tests or studies of any kind in connection with your work in this case; isn't that true?

A. That is correct.

Q. You did no research into methods used in medical or epidemiological scientists for assessing causal relationships in connection with your work in this case, correct?

A. No new work, yes, that's correct.

Q. And, Professor Trimble, in your entire report, am I correct, there is not one relative risk calculation anywhere in it, correct?

A. That is correct.

Q. There is not one odds ratio calculation anywhere in it, correct?

A. That is correct.

JUDGE SARIS: Excuse me. You know, for this to be helpful to me anyway, you've got to explain what this means. You have submitted hundreds and hundreds and hundreds of pages of reports and exhibits and briefing; and while I think the both of us have tried to read most of it, we're not

experts. So if you want this to be helpful to us, you need to do more with this. Okay?

MR. HOOPER: I will.

JUDGE SARIS: So what does that mean?

MR. HOOPER: I will sure try. I will sure try.

Q. Professor Trimble, are you familiar with the concept of a relative risk calculation?

A. The relative risk is an epidemiological statistic. I am not an epidemiologist.

Q. And a relative risk is one of the two main calculations that are used to assess the strength of an association that Mr. Finkelstein talked about; isn't that true?

A. I'm not an epidemiologist, but if you say that is the case, I will accept it for epidemiology. I am not an epidemiologist. I do not know their main -- I don't know that it's true that they're their main methods. I'm not an epidemiologist.

Q. Sir, do you know whether an odds ratio is a mathematical expression used in epidemiology to assess the strength of an association?

A. I believe it is.

Q. And you have calculated no odds ratio in your work in this case, correct?

A. It is not correct now in the sense that I have calculated some odds ratios in relationship to the dose

response relationship of side effects to the doses of gabapentin. So I have actually calculated some odds ratios since you asked that question, but I have done that since our depositions, between then and now.

Q. Sir, there is no odds ratio calculation that purports to measure the strength of an association in your expert report in this case, correct?

A. That is a correct statement.

Q. And, sir, when we deposed you for two days last October, you offered no calculation of any odds ratio to measure the strength of an association between gabapentin and any form of suicidality, correct?

A. That is correct, which is why I have now done the odds ratio calculations that you suggested I should have done before.

Q. You were first approached in this litigation in September, 2005, sir?

A. Perhaps 2005. I believe that's correct.

Q. Stefan Kruszewski, another one of the plaintiffs' experts, approached you?

A. That's correct.

Q. And as you worked on your report in this case, the Finkelstein firm sent you various documents and written materials, correct?

A. That is correct.

Q. The Finkelstein firm sent you both Pfizer- and FDA-authored documents, correct?
A. That is correct.
Q. Apart from what the Finkelstein firm sent to you, you never requested any documents yourself from the FDA or any European regulatory authorities, correct?
A. That is correct.
Q. You wrote a first draft of your general causation report, and you sent it to Mr. Finkelstein, correct?
A. That would be correct, yes.
Q. And you met with Mr. Finkelstein in New York at some point or some time that you couldn't remember at your deposition, correct?
A. That's correct.
Q. And you threw away the first draft of your report, right, sir?
A. I was consigned to the -- yes, exactly, yes, correct.
Q. And you prepared a second draft of the general causation report?
A. That's correct.
Q. You met then with various members of Mr. Finkelstein's firm, including their not-lawyer employee, Mr. Keith Altman, at a roundtable to discuss your second draft report, correct?
A. After it was submitted to Mr. Finkelstein, that's correct.

Q. And like the first draft, the second draft is one that you threw away as well, correct?

A. You may be correct. I accept that may be correct, yes.

MR. HOOPER: Slide 5.

Q. Professor Trimble, in terms of identifying any scientific method that you claim to have followed in developing your general causation opinions in this case, you told me at your deposition that you followed a chapter on causation that you wrote in a book entitled Somatoform Disorders, correct?

A. That is correct.

MR. HOOPER: Your Honor, may I approach the witness?

Q. Is that a copy of the book you referred to in your deposition, sir? Is that a copy of the book, Professor?

A. Oh, it is, yes.

JUDGE SARIS: What does "somatoform" mean?

THE WITNESS: Your Honor, this book was written specifically to help lawyers in certain cases that I also happen to know a lot about and have dealt with in clinical practice. These are people who present with medically unexplained symptoms. Now, the old-fashioned term for that was "hysteria," which may ring a bell with your Honors; but in a medical context, it refers to people who present to doctors, but particularly neurologists, with, for example, a

paralysis of the arm where no neurological abnormality can be found. And so the term "somataform" is an unfortunate term. It comes from the American Diagnostic and Statistical Manual of Mental Disorders, and it refers to those people who present with somatic symptoms where there's no underlying neurology. And this is a very, very difficult area of causality, and my chapter on causality here relates to the difficult issue as to whether things are conscious or unconscious, which of course is something which is very predominant in the civil but also in the criminal courts. So I hope your Honors understood the term.

Q. Professor Trimble, this book is not cited or mentioned anywhere in the general causation report that you wrote in this case, is it?

A. Well, no.

Q. The first time that you claimed you had followed a method set out in that book was during your deposition, correct?

A. That's correct.

Q. And that book Somatoform Disorders was not subjected to the peer-review process that scientific journals commonly require prior to publication, was it?

A. Books generally are not. This is published by Cambridge, and Cambridge will only accept books after they've read and had the manuscripts reviewed by reviewers. And part

of this was reviewed by reviewers, which is a kind of peer-review process, but it's not the same as a journal review process.

JUDGE SARIS: Is the chapter you relied on in the record? Did you attach it to your report?

THE WITNESS: No, your Honor, because it was not in my report. It came out in the deposition.

JUDGE SARIS: So are you marking it now?

MR. HOOPER: Your Honor, I'm about to authenticate it and want to try to move to enter it momentarily.

JUDGE SARIS: The book?

MR. HOOPER: The chapter, the certain chapter.

Q. Professor Trimble, as you told me, your book was intended to help the legal profession understand more about causation in relation to medical events, correct?

A. Somatoform disorders, medically unexplained symptoms.

Q. Would you look at Tab B in your materials, sir.

MR. HOOPER: And if I may approach the witness?

JUDGE SARIS: Sure. You don't have to keep asking.

MR. HOOPER: Thank you.

Q. And a copy of that, Professor Trimble. And would you confirm that Tab B and the document I've just handed you are accurate copies of Chapter 9 of your book Somatoform Disorders entitled "Causation and the Question of Consciousness"?

A. That is correct, yes.
Q. And that chapter entitled "Causation" is the one that you referred to in your deposition as the method you'd followed, correct?
A. My understanding of causality, yes.
Q. It's the only chapter entitled "Causation" in the book, isn't it, sir?
A. That's correct, yes.
MR. HOOPER: And, your Honor, I move to admit this copy of Chapter 9 of Professor Trimble's book Somatoform Disorders: A Medicolegal Guide.
MR. FINKELSTEIN: No objection.
(Exhibit 1 received in evidence.)
MR. HOOPER: Slide 8, please.
Q. In fact, Professor Trimble, this book chapter that you claim to have followed in your work in this case discusses causation in terms of philosophical theories, such as the writings of David Hume and John Stuart Mill and Immanuel Kant?
A. Nietzsche.
Q. Nietzsche, Aristotle?
A. Yes.
Q. And it also in a subsequent section discusses legal doctrines such as res ipsa loquitur and foreseeable intervening causes, correct?

A. Yes, that's correct.
Q. And you have some case analyses of short summaries of legal decisions and legal tests for causation in the book; is that right?
A. That's correct, that's correct.
Q. The term "biological plausibility" doesn't appear anywhere in that chapter, does it, Professor Trimble?
A. Well, that would be correct.
Q. And the truth is, Professor Trimble, that Chapter 9 of your book doesn't set out any scientific method or any scientific protocol for analyzing scientific data for the purpose of assessing general causation between a drug and an adverse event, does it?
A. That would be correct, in the context of who the book was written for and why it was written.
Q. Did you recognize the slide that Mr. Finkelstein put up in his presentation that had the bullet points of nine factors that he said you applied that began with strength of association and included among them consistency, biological plausibility, and so forth?
A. I did.
Q. Do you recognize those, sir, as what are commonly known as the Bradford Hill criteria?
A. Those are commonly referred to as Bradford Hill principles or propositions. I'm not sure they're criteria in

the sense that the DSM criteria might be used for making diagnosis, but. . .

Q. They were first promulgated by Sir Austin Bradford Hill, a British scientist, in 1965 in the Proceedings of the Royal Academy of Medicine; is that correct, sir?

A. I believe that's correct, yes.

Q. And the Bradford Hill criteria, are you aware, sir, that the Bradford Hill criteria are also set out in the Reference Manual on Scientific Evidence published by the Federal Judicial Center in this country?

A. I am not aware of that.

Q. The list of the Bradford Hill criteria are not in Chapter 9 of your book; is that correct?

A. The viewpoints, I think actually is what Bradford referred to them as, are not generally principles that are laid out in a book such as I would be writing in terms of trying to inform a medical and a legal audience about the complexities of consciousness and causation in difficult areas such as somatoform disorders.

Q. Professor Trimble, what Chapter 9 does not do is set out a method for assessing scientific data to determine whether a drug causes an adverse event, does it, sir?

A. The book has nothing to do with drugs whatsoever.

MR. HOOPER: Slide 9, please.

Q. Professor Trimble, at Page 41 of your report, again

Tab A in the binder, you opine that "Prescription of Neurontin has been shown to lead to increased levels of GABA in the central nervous system of healthy volunteers and patients prescribed the drug," correct?

A. Excuse me, Page 41?

Q. Yes, sir.

JUDGE SARIS: It's also up on the screen if you --

THE WITNESS: Oh, thank you.

Q. It's right in the middle of the page.

A. Yes, that is correct.

Q. And you opine further that, in your opinion, gabapentin decreases serotonin and norepinephrine activity, correct?

A. That is correct.

Q. For the benefit of those who may not be familiar with those terms, let's walk through them. GABA is a substance that is naturally found in the central nervous system, correct?

A. That is correct.

Q. It is an acronym for gamma-aminobutyric acid, correct, sir?

A. That's correct.

Q. And gamma-aminobutyric acid, or GABA, is one of the body's and brain's natural signaling chemicals, correct?

A. That's correct.

Q. Sometimes called a "neurotransmitter"?

A. That's correct.
Q. And GABA is a ubiquitous neurotransmitter in that it is found widely throughout the body, correct?
A. Well, let's say the brain for these purposes.
Q. And I believe you told me at your deposition that 60 to 70 percent of the neurons have GABA activity?
A. The majority of neurons within the brain -- there's the nerve cells within the brain -- have something to do with the action of GABA.
Q. And Professor Trimble --
JUDGE SARIS: So when you use GABAergic throughout, that means what?
THE WITNESS: Well, let me be very clear, your Honor, what I'm referring to by that. I'm referring to something which increases somehow, ergic, the agonist, increases the effect of, increases either the turnover of it -- in other words, increases the amount that's produced -- or it increases the effect of that chemical at the point at which it acts on the next stage in the system. In other words, a neurotransmitter is released from a neuron at a point referred to as the synapse, and then the neurotransmitter will flow from the synapse and influence the next station, if you like, in the messaging system, which is often called the postsynaptic receptor.
JUDGE SARIS: And you say that is secure that it's

GABAergic, secure where? Is that in peer-reviewed literature?

THE WITNESS: It is commonly used by epileptologists. I'm an epileptologist. It's commonly used by biological psychiatrists.

THE COURT: So commonly used means it's common in the field to conclude that it's GABAergic?

THE WITNESS: That's correct.

JUDGE SARIS: Now, are you disputing that?

MR. HOOPER: We do disagree with the definition, and we'll cover that in --

JUDGE SARIS: No, but do you disagree that it's generally accepted in the field that it increases the amount and effectiveness of the GABA, that gabapentin does?

MR. HOOPER: It depends on where. It's more complicated than that, your Honor. There are certainly peer-reviewed literature that --

JUDGE SARIS: That would say this, right?

MR. HOOPER: Whole brain, but we differ from thereon, and we'll make that clear throughout our presentation.

JUDGE SARIS: You know, but I thought your briefs were, like, going in the night. I didn't even know where you agreed and you didn't agree. So at least for purposes of this, it's accepted, as I understand it, in the literature

that it increases the amount and effect of GABA in the brain, gabapentin?

MR. HOOPER: We dispute that as you just said it, your Honor, we do.

JUDGE SARIS: Well, did I say that correctly, Dr. Trimble?

THE WITNESS: Your question, your Honor, was the meaning of the word "GABAergic"?

JUDGE SARIS: Right, but I'm now asking a second question, which is, is that description of what it does, there are increased levels of GABA in the CNS, is that accepted in the peer-reviewed literature?

THE WITNESS: It's very central to the case, your Honor, and thank you for asking the question. It is undisputed, I thought, that with spectroscopy -- Mr. Finkelstein already mentioned this -- when you actually measure the amount of GABA in the brain, you can reliably, and it has been shown in more than one experimental center, show an increase in GABA in the central nervous system of humans.

THE COURT: Of?

MR. FINKELSTEIN: Of humans.

THE WITNESS: Of humans. I'm sorry, of the human brain.

JUDGE SARIS: And do you dispute that?

MR. HOOPER: Yes, and --

JUDGE SARIS: All right, I just want to understand the areas of dispute. You disagree with what he just said?

MR. HOOPER: We do, your Honor, and may I take just a moment and articulate our position, and we'll elaborate on it with witnesses when they come up?

JUDGE SARIS: It's your turn.

MR. HOOPER: Okay, sure. In our view, your Honor, as we'll get into further, the studies that Professor Trimble just referred to, and we're about to go right to them, measure whole brain GABA. They look at a whole head. They don't tell you anything about whether the GABA is moving from neuron to neuron or whether it is active. To look at those studies and infer that they are GABAergic in the sense of affecting the function of GABA, as opposed to simply the amount of it, is like looking at the fuel gauge --

JUDGE SARIS: All right, so that's the distinction. I don't want to go off on this, but at least there's an agreement, I'm sounding like -- just I have to understand it -- that there's an increase in the amount of GABA in the whole brain, but you might disagree on what the effect of that is?

MR. HOOPER: Perfectly said, your Honor.

JUDGE SARIS: Yes, but, you see, I can't get this from the briefs. It's useful sometimes to say where you

agree. All right, so there's an agreement that there's an increase in the amount of GABA in the brain in gabapentin, but not as to what the effect of that is?

MR. HOOPER: Correct, your Honor.

JUDGE SARIS: Thank you.

MR. HOOPER: Slide 10, please.

Q. Professor Trimble, from these effects on the neurotransmitters, GABA and serotonin, you contend that the medication leads to the onset of negative mood states, which will lead to or enhance suicidal ideation and acts, and is associated with completed suicides, as stated in your report, right, sir?

A. That is correct.

Q. Professor Trimble, you have no idea what the normal GABA level is in a human brain; is that correct?

A. Well, I do now. You asked me this in my deposition, and I did not have the figure on the tip of my tongue, but it is available.

Q. And you do not state one in your report, do you, sir?

A. I did not at that time, no.

Q. And you do not know a range within which GABA levels would fall in normal healthy adults, do you, sir?

A. Well, it's available, as I pointed out.

JUDGE SARIS: Well, what is it?

THE WITNESS: Well, it's micro amounts per liter,

and it's in the region of 1, 2 -- 1.5, I believe, but it varies between individuals. But it's not -- it's a figure which is readily available in Petroff's study in the paper.

MR. HOOPER: Slide 11, please.

Q. Professor Trimble, do you recall that you explained to me in your deposition that the brain contains a small collection of neurons, nerve cells called the raphe nuclei, that are, as you described it, the nuclei where the serotonin comes from, correct?

A. Correct.

Q. And we agree on that, that serotonin is generated by the raphe nuclei?

A. That is correct.

Q. And the raphe nuclei, as you told me, are the center from which the main serotonin pathway emerges, correct?

A. That's correct.

Q. And we agree on that?

A. That's correct.

Q. And you explained in your deposition that experimental researchers in the 1980s were able to place GABA in the neuron collections, the raphe nuclei, where the serotonin comes from, and show a direct effect that GABA had upon the release of serotonin, correct?

A. That is correct.

MR. HOOPER: And Slide 1, please.

JUDGE SARIS: Wait, wait. This is the heart of it. So, in your view, it inhibits the release of serotonin, right?

THE WITNESS: Your Honor, that is quite correct. The experiments done well before this legal case show that if you put through a pipette some GABA onto these serotonin-generating cells, the turnover of the serotonin would be decreased. So increasing GABA action at this site was shown to decrease the turnover of serotonin.

JUDGE SARIS: Now, was this in the peer-reviewed literature?

THE WITNESS: It is, your Honor.

JUDGE SARIS: Do you disagree with that?

MR. HOOPER: No, your Honor.

JUDGE SARIS: What?

MR. HOOPER: No, no.

Q. Professor Trimble, you also said that there are other studies that show that when pathways going into the raphe nuclei are stimulated, those GABA pathways, when they're stimulated, there is a decrease of serotonin output, correct?

A. That is correct.

Q. Because the raphe is where the serotonin is produced and generated to the rest of the brain, correct?

A. That is correct.

Q. And, Professor Trimble, when you sat for your deposition

in this case, you told me that you were not aware of any studies in which anyone has measured GABA level changes in the raphe after gabapentin, Neurontin, administration, correct?

A. That is correct. At the time those studies were done, Neurontin was not available. Other GABAergic agents which were being tested as antiepileptic drugs were used.

Q. Now, Professor Trimble, at Page 24 of your report, the bottom paragraph, third line, you cite a 2000 study by Mr. Petroff and colleagues, correct?

A. That is correct.

Q. The Petroff group used technology called a nuclear magnetic resonance spectrometer, NMRS for short, to measure changes in GABA levels after administration of gabapentin to six epilepsy patients after an initial dose, and then four of them after several months of taking gabapentin, correct?

A. That is correct.

MR. HOOPER: Slide 17.

Q. And the Petroff group, using NMRS technology, after 30 to 60 minutes measured what they described as a rapid increase in GABA, correct?

A. That is correct.

Q. And in the four patients that were studied after several months of gabapentin therapy, the Petroff group measured levels that were down somewhat from that initial reading but

remained nonetheless 55 percent higher on average than at baseline, correct?

A. That is correct.

Q. And these results together with the Kuzniecky study, which we'll get to momentarily, are the kind of GABA elevations that are associated with gabapentin use that you refer to in your report, correct?

A. That's correct.

MR. HOOPER: Slide 18, please.

Q. The adverse events that were reported for these patients in this peer-reviewed published study are not mentioned in your report, are they, Dr. Trimble?

A. Not in -- the adverse effects with gabapentin --

Q. In the Petroff --

A. No, no. No, this has to do with the imaging data only.

Q. In fact, the Petroff study said that of the six patients, five experienced no acute side effects with these elevated levels of GABA. One developed ataxia, which is incoordination, correct?

A. That's correct.

Q. Sedation and nystagmus, eye movement that resolved overnight, correct?

A. That's correct.

Q. And after months of treatment and rechallenge at the end, no side effects were noted?

A. That's correct.

JUDGE SARIS: So what was the point of this study?

THE WITNESS: Well, your Honor, at the time the study was carried out, it was very important for antiepileptic drug development to understand how it was that you could turn off seizures in people with epilepsy. GABA, as we've heard, is an inhibitory transmitter. And drug development was very interested in looking at drugs that increased GABA in the central nervous system, and there were several drugs that were looked at by industry which seemed as if they would increase GABA.

Now, the development of magnetic resonance spectroscopy allowed for the first time the measurement of brain chemicals. So I'm sure your Honor is familiar with the idea of brain imaging with magnetic resonance imaging -- it's in all of the newspaper -- but you can get a perfect anatomical picture of the brain. With spectroscopy, you are able to add a measurement of the chemicals within certain areas of the brain. And so the purpose of this study was to see if gabapentin, which was developed as a GABA agent, a GABA agonist, a drug which would increase the GABA effect, altered GABA in the central nervous system. And it was preceded by a study of another GABA agonist called vigabatrin, and it was shown that that other GABA agonist, which was an effective antiepilepsy drug, increased GABA in

the central nervous system.

And so the manufacturers of Neurontin wanted to know if their drug would also increase GABA within the central nervous system. And that was why the study was done, and I was there when the results were very first presented in Munich, I can't remember how many years ago now. But it came as considerable relief to perhaps understand how it was that gabapentin might have an antiepileptic effect by increasing GABA in the same way that, for example, vigabatrin had done previously.

MR. HOOPER: Slide 19, please.

Q. Professor Trimble, the second study you cited at that same page in your report is a study by Kuzniecky and colleagues in 2002, correct?

A. That is correct.

Q. And I've got that at Tab D in your binder, if you'd like to see the whole copy. The full paper is at Tab D.

MR. HOOPER: Slide 21.

Q. This study, similarly to the Petroff study, used NMRS technology to measure GABA level changes with gabapentin administration, correct?

A. That is correct.

Q. And this study specifically looked at six healthy adults who took gabapentin as well as six who took a different drug, topiramate, and five who took a third drug, lamotrigine,

correct?

A. Correct.

MR. HOOPER: Slide 22, please.

Q. And in the six gabapentin subjects, the Kuzniecky group measured a 48 percent increase in GABA after the first acute dose, right, sir?

A. I'll accept the figure. I just don't have it --

Q. From the abstract?

A. Yes, from the abstract.

JUDGE SARIS: If you look up on the screen, they've pulled out what they are focusing on.

A. Yes, that is correct.

Q. And, Professor Trimble, after four weeks, the Kuzniecky group measured GABA levels to be approximately 25 percent higher than baseline in the gabapentin subjects, correct?

A. Yes, I accept that.

MR. HOOPER: Slide 23.

Q. And Kuzniecky, much Luke Petroff, also reported that there were no serious side effects. One individual had transient ataxia, the same incoordination we saw in one patient in the Petroff study, and the others listed are from the other drugs?

A. This is one out of six?

Q. Six.

A. That's nearly about 20 percent, but it's quite a high

percentage with side effects.

Q. None had depression or suicide of any kind, sir, did they?

A. Oh, no, of course not.

Q. And you don't mention the side effects with these patients with the 25 percent and 48 percent elevated GABA levels in your report, do you, sir?

A. Well, since you draw attention to them, it seems like a very high percentage of central nervous system effects, with ataxia, with somnolence, dizziness, slow thinking, drowsiness. Since you draw my attention to them, they're there, but I haven't discussed them in the section of my report that specifically deals with the biochemical GABAergic or the increase in GABA in the central nervous system.

JUSTICE FRIEDMAN: Excuse me. Professor, does your report cite any studies that discuss the side effects of increased GABA in the brain or in the central nervous system?

THE WITNESS: Yes, your Honor. I discuss the effects of GABA on the central nervous system specifically in relationship to antiepileptic compounds that increase GABA in the central nervous system, and there is a section on that.

JUSTICE FRIEDMAN: But do you discuss any studies or peer-review literature that analyzes the effects of increased GABA? Is there a section of the report that is

specifically devoted to that?

THE WITNESS: Yes, there is, your Honor, yes.

Q. Professor Trimble, antiepileptic drugs generally have been around for decades, correct?

A. Since the 1920s.

Q. Gabapentin was developed in the 1970s, correct?

A. That is correct.

Q. Tested through the 1980s and into the 1990s?

A. Correct.

Q. It has been approved and used, marketed in the United States since 1993, correct?

A. Correct.

Q. Do you have any basis to dispute that gabapentin has been used for in excess of 15 billion patient days of therapy?

A. I accept your figure.

JUDGE SARIS: What was the number?

MR. HOOPER: In excess of 15 billion patient days, approximately, your Honor.

Q. And, Professor Trimble, isn't it true that in all of the peer-reviewed scientific literature in the world, there is not one scientific study that purports to say that it has demonstrated that gabapentin causes suicide?

A. Well, that is correct.

JUDGE SARIS: So one thing that's been confusing

me, what do you consider the FDA alert to be?

THE WITNESS: Thank you, your Honor.

JUDGE SARIS: In the scientific world?

THE WITNESS: I think Mr. Hooper was not referring to the FDA report in terms of his question about peer-reviewed literature.

I accept in its entirety that the FDA, independent of this litigation or my views or work on GABA and serotonin, have detected a signal that antiepileptic drugs, anticonvulsant drugs, are associated with suicide acts, ideation, or completed suicide.

I take the FDA's various documents, announcements, and the more recent statements to vindicate entirely my view, which, of course, starts from a different end of the spectrum. I'm not an epidemiologist. I'm starting at what happens within the brain when you give drugs that alter key transmitters that alter behavior. That's where I come from, starting within the brain as a neurologist. But the FDA epidemiological data, as far as I can see, entirely vindicates the views that I've put forward; but my views were put forward before the FDA reached the conclusions that they did.

JUDGE SARIS: Well, do you consider what they did an epidemiological study?

THE WITNESS: I believe it to be so.

JUDGE SARIS: And is that something that would be accepted by people in the field as reliable? By you, by you?

THE WITNESS: Your Honor, I accept that the FDA have a much more powerful team of statisticians and epidemiologists working with them than I would have access to. I accept that the FDA do not put out pronouncements like this without having gone into the whole area extremely thoroughly.

JUDGE SARIS: And as I understand, the point Pfizer is making is that it's the first of its kind. I mean, there's no other epidemiological study that's gone through peer review, right? Is that your basic --

MR. HOOPER: Yes, your Honor.

JUDGE SARIS: There's nothing in the literature that has done this kind of an epidemiological study, is that right?

THE WITNESS: I believe that's correct, your Honor. And the FDA have done a meta-analysis -- in other words, collected data on a large number of patients on a large number of drugs -- and reached the conclusion that they have, which is that these antiepileptic drugs lead to an increased risk for suicide acts.

JUDGE SARIS: And your point, as I take it, is that there's nothing in what you would call the peer-reviewed

literature that does this kind of an analysis?

MR. HOOPER: It is, your Honor, and we also dispute that characterization of what the FDA alert and statistical analysis mean, and we'll cover that in great detail.

JUDGE SARIS: I understand. We need to come back to that, but I --

MR. HOOPER: We will. Slide 24, please.

Q. Professor Trimble, we were talking about elevated levels that you relied on in the Petroff and Kuzniecky study. Tab E is a copy of a study conducted right here in Boston by Streeter and colleagues entitled "Yoga Asana Sessions Increase Brain GABA Levels: A Pilot Study" published in 2007, correct?

A. That is correct.

Q. The first time you saw and read this study, Professor, was when I showed it to you at your designation, right?

A. That is correct.

MR. HOOPER: Slide 25.

Q. This was a study done here in Boston at Boston University School of Medicine, McLean, Harvard, and the Boston VA by a research team from those institutions, correct, sir?

A. That's correct.

Q. And this study, like the Petroff and Kuzniecky studies you cited, it also used this MMRS energy technology to

measure brain GABA levels, did it not?

A. That's correct.

MR. HOOPER: Slide 26.

Q. And they found that there was a 27 percent increase in GABA levels in people who practiced yoga for an hour, correct, Professor Trimble?

A. That's not correct. That is one of the conclusions from this study, and I went through this in my deposition, but what this shows, your Honor, is that if you have a group of people, a small group of people doing exercises for an hour and another group of people sitting reading, you show differences in brain GABA. If I do exercises for an hour, I will show differences in brain GABA because GABA is ubiquitous and it has many actions. And I did explain in the deposition when I read this paper that there's a big difference between physiologically doing something for an hour and altering endogenous activity of GABA, for example, in the central nervous system artificially, as you do with drugs. But this paper tells me nothing other than if you do exercises, you can show an increase in brain GABA.

JUDGE SARIS: You might get depressed, huh?

THE WITNESS: Excuse me?

JUDGE SARIS: If you exercise too much, you might get depressed.

THE WITNESS: The assumption that this somehow

vindicates -- I'm sorry -- somehow suggests that alteration of brain GABA in a different setting has anything to do with the importance of yoga as an antidepressant is, quite frankly, bizarre. This was a one-hour study, and the areas of the brain looked at were not the same, by the way, as were looked at by the other studies that we've talked about. They looked more specifically in areas of the brain that have to do with motor activity, the basal ganglia areas.

Q. Professor Trimble, if I could direct your attention to what these researchers from Harvard and Boston University and McLean said, the second sentence of their conclusion, tell me if I'm reading correctly. This is 27 percent increase. "This suggests that the practice of yoga should be explored as a treatment for disorders with low GABA levels, such as depression and anxiety disorders." Is that their conclusion, Professor Trimble?

A. It's one that I can't take seriously, but it's the conclusion.

I should like to draw your attention, your Honor, to the journal that this was published in, and the reason I haven't read it is because I am not a regular subscriber to the Journal of Alternative and Complementary Medicine.

Q. The fact is, Dr. Trimble, that many agents that are used to treat depression and suicidality, agents that you yourself have subscribed many times, are known to increase GABA

levels; isn't that true?

A. If you'd like to list them for me because I do not know of any study which reliably shows a drug which increases GABA activity in the central nervous system is antidepressant; but if you'd like to tell me the drugs you're thinking about, I will try to be more specific.

Q. I sure will. How about lithium? Does lithium raise GABA levels?

A. Lithium does many things. To my knowledge, it doesn't have an effect. I don't think it's been looked at with spectroscopy, and I don't believe the GABA story comes into the lithium effect.

Q. Do you know one way or the other, Professor Trimble, whether or not there is peer-reviewed research demonstrating that lithium elevates GABA levels?

A. I do not believe that lithium elevates GABA levels.

Q. Electroconvulsive therapy, or ECT, is widely recognized as the most effective treatment for imminently suicidal patients, isn't it, Professor Trimble?

A. That is correct.

Q. It is also widely used, to the extent that it is used, for treatment of depressive disorders?

A. That is correct.

Q. Severe cases of depressions in particular, correct?

A. That's correct.

Q. And ECT elevates GABA levels, doesn't it, Professor Trimble?

A. Of course it elevates GABA levels because you have a seizure, and the brain has to cut off seizures. Otherwise you'd have status epilepticus, and the patient would die. So the brain has its own endogenous mechanisms to cut off seizures. So when you give an artificial seizure, then of course you see a rise in GABA, and that would be expected from what we know about the physiology of seizures. But the idea that the increased GABA is the antidepressant effect I'm afraid is one which is not accepted. I mean, we do not know how ECT works, but it's not by increasing GABA.

Q. Selective serotonin reuptake inhibitor, or SSRI, antidepressants elevate GABA, don't they?

A. It depends which SSRI you might be talking about. There is a spectroscopy study which shows you get a rise in GABA with SSRI, with -- I think it was, fluoxetine, Prozac. But, again, that says nothing at all about the importance of that in terms of the antidepressant effect, if that's what you're suggesting.

Q. Professor Trimble, at Page 27 of your report you refer to a study by Dr. Eleanor Ben-Menachem and her research team that was published in 1992, correct?

A. That's correct.

Q. And you indicate there that she reported on the effects

of single doses of gabapentin on cerebrospinal fluid monoamines. That's serotonin and norepinephrine, correct?

A. That is correct.

Q. And that gabapentin led to an increase in the breakdown products of serotonin, suggesting acute increases in serotonin turnover, correct?

A. That is quite correct.

Q. Which is the exact opposite of what Mr. Finkelstein had on his slide in the opening when he said that this drug reduces serotonin turnover, isn't it?

A. It's not at all. This is -- again, your Honor, there's a big difference between what happens immediately you give a drug and what happens some time later. So if you give, for example, a drug -- I'm sure you've heard of dopamine and Parkinson's disease, for example -- if you give a drug that blocks dopamine receptors, if you give a drug that blocks dopamine receptors, the brain responds to that by a huge outflow of the transmitter. It says, "Hey, everything's blocked here," and you get an outflow of the transmitter. So you give a drug, and you get the paradoxical effect immediately, and then the system reverts to a different homeostasis.

Now, this is entirely what you would expect with a drug, that you get immediately one effect, but then after a period of time you get an alternative effect. And

Dr. Ben-Menachem, who I know very well and have discussed these data with, also looked at another drug which increases GABA, vigabatrin, and showed the same, that immediately acutely you get an acute increase, but then chronically -- in other words, after giving the drug chronically -- you get a depletion. And so --

JUDGE SARIS: So can I ask, increase in turnover just means increase in serotonin?

THE WITNESS: Increase in, yes, there's an outflow of serotonin. And what happens is, you get the outflow of serotonin. The serotonin becomes depleted. In other words, the brain runs out of not all but its stores of serotonin. There's an adjustment that happens. And then chronically, after longer-term treatment, you show a decrease of the serotonin turnover, which is indeed what Dr. Ben-Menachem showed in her later paper of 1995.

MR. HOOPER: We're about to get that, Dr. Trimble, if you're ready, Judge.

Q. You wrote in your report in this case, the effects of chronic administration in humans of gabapentin, the situation you just described, had not been studied. That's false, correct?

A. You very kindly in my deposition drew my attention to the 1995 paper, which I had -- I wouldn't say not -- I had just not come across this.

Q. It's at Tab F in your binder, Doctor.
A. Yes.
Q. You recognize it as Dr. Ben-Menachem's 1995 paper entitled "Seizure Frequency and Cerebrospinal Fluid Parameters in a Double-Blind Placebo-Controlled Trial of Gabapentin in Patients with Intractable Complex Partial Seizures," correct?
A. That's correct.
Q. This is a study of gabapentin in chronic administration; namely, three months administration, correct?
A. That's correct.
Q. This study is cited nowhere in your report, is it professor?
A. No. That is correct. That is correct.
JUDGE SARIS: Well, what does it say?
MR. HOOPER: This, your Honor.
Q. Professor Trimble --
THE WITNESS: Sorry, your Honor. Did you ask a question?
JUDGE SARIS: Are you going to go through it?
MR. HOOPER: Yes. Yes, your Honor.
Q. Professor Trimble, as stated in the abstract of Dr. Eleanor Ben-Menachem's 1995 study, "Cerebrospinal fluid was analyzed for concentrations of gabapentin, amino acids including GABA, homovanillic acid, HVA, and

5-hydroxyindoleactic acid," or 5-HIAA." And let me stop right there.

Gabapentin is the drug we hear about today, correct?

A. That is correct.

Q. GABA is the neurotransmitter we've been talking about, correct?

A. That's correct.

Q. Homovanilic acid is the principal breakdown product of the monoamine neurotransmitter norepinephrine, correct?

A. Dopamine.

Q. Or dopamine, I'm sorry, dopamine. And 5-HIAA is the principal breakdown product of serotonin, correct?

A. That is correct.

Q. And the very next sentence says, "The results indicate that there were no changes in the selected amino acids, HVA or 5-HIAA, after gabapentin treatment." Did I read that correctly, Professor Trimble?

A. You read that correctly. And in the deposition, I draw your attention to Figure 5, which I imagine you have here.

Q. Feel free to discuss it. The Judge can see what you're looking at.

JUDGE SARIS: Yes, I've just gone there.

THE WITNESS: Your Honor, the whole point about the discussion here is whether or not, as with other GABAergic

agents, when you give the drug chronically, you get a decrease in the turnover of the breakdown product of serotonin. In other words, because the breakdown is -- because the release is reduced, you don't see so much metabolic breakdown, and this is what 5-HIAA is. It's the breakdown product of serotonin.

So just to recap, we're looking here at the breakdown product of serotonin. So a decrease of this would reflect a decreased serotonin in the human brain. And it merely shows you that with gabapentin, after three months, there is a decrease, particularly with 1,200 milligrams.

Now, the difficulty, your Honor, is that it's only three patients that are cited, and you cannot do effective statistics on such small numbers. But -- and I'm afraid the photocopy is a poor one -- but the little bars which straddle the mean there are a reflection of the variance of the data. So it's quite close together. You can't do statistics on it, but it looks to me, compared with the placebo, which is on the far left where you see an increase, that I would say that that reflected a decrease. Now, it's not statistically significant because nobody would have done statistics or she didn't do statistics on those three.

JUDGE SARIS: So you're saying a decrease over the three months but not right away?

THE WITNESS: Well, it's immediate -- the first

paper Mr. Hooper referred to showed there was an increase, so you get an outflow.

JUDGE SARIS: I just want to make sure we're looking in the same place. This is Figure 5?

THE WITNESS: This is Figure 5, which is three months later. So I'm saying that at three months you don't see an increase, but you see a decrease. This is with long-term treatment, you see a decrease of serotonin breakdown products in the human brain, as measured in the cerebrospinal fluid. But you can't effectively do the statistics here because there's only three patients. But you can see that the spread of the data by that little mark above and below the mean is really quite narrow, but it's not significant, and Dr. Ben-Menachem says it's not shown to be -- well, not shown to be different. And that's because it's not statistically different. But she didn't do statistics on it because if you look at Table 1 where all of the CSF amino acids are looked at, she didn't include HVA and 5-HIAA there.

So the importance of this study, which I did go through in my deposition, is that it supports the view -- it's not conclusive -- it supports the view that in the human brain, with chronic gabapentin treatment, you get down regulation of activity of this key neurotransmitter for mood regulation; namely, serotonin.

Q. Professor Trimble, did you just tell Judge Friedman and Judge Saris that you couldn't do statistics because there was only an N of 3, or three patients?

A. I believe you can do statistics on that level, but I believe that Dr. Ben-Menachem did not do statistics on that, probably because there was an N of 3, because she did statistics on all of the others. But this was 21, I think, cases, so why she didn't do statistics on those, I do not know.

Q. Professor Trimble, when you look at Figure 5, do you see those bars?

A. Oh, well, yes --

Q. Those error bars?

A. Yes.

Q. Isn't that statistics?

A. I beg to be corrected. Mr. Hooper is quite correct. They obviously --

Q. Did statistics?

A. -- looked at some statistical figures, but they don't provide the statistical significance. They don't provide what we would like to see; namely, the confidence intervals, et cetera.

Q. And, Professor Trimble, did you just tell Judge Saris and Judge Friedman that there were only three patients examined for this 5-HIAA increase?

A. Well, the graph is N of 3, as far as I can tell. I'm sorry, N of 6. I beg your pardon. And I can't quite read the photocopy here, but it's N of 3 after -- what I was looking at was N of 3, which is after -- yes, at the higher dose.

Q. Let's look at --

JUDGE SARIS: Well, what do you think it is? It was N of 6 for the placebo.

THE WITNESS: Yes.

JUDGE SARIS: And N of 3 for each of the two different dosage levels.

THE WITNESS: There are two different doses of the drug, your Honor.

JUDGE SARIS: Right.

MR. HOOPER: Your Honor, it's stated right in the report. We'll look at it now if you'd like.

JUDGE SARIS: I don't want to take your time. You're running out, so --

MR. HOOPER: That's fine. It will be fast.

Q. Professor Trimble, if you look at Page 294, doesn't Dr. Ben-Menachem explicitly say eleven patients with 900 milligrams of gabapentin and three with 1,200? The middle set of columns, eleven patients; the second set with three, correct?

A. I'm looking at Figure 5.

Q. And do you see the number, and don't they correspond to the doses?

A. But it's 900 milligrams. The photocopy is rather bad, but it says "900 milligrams, N equals 3" in Figure 5.

Q. Do you see Section 3.2 of the text, Professor Trimble? Eleven patients with 900 milligrams of gabapentin and three with 1,200. The GABA levels were not affected by chronic gabapentin treatment, 3 and 4. The same was found for 5-HIAA and HVA, correct?

A. That is correct, but it doesn't correspond to the figure which I am looking at.

Q. Professor Trimble, again in Figure 5, if you look at the leftmost set of bars in Figure 5, there is a label under them that says "Placebo," isn't there?

A. Yes, that is correct.

Q. And the difference in height between those two bars, black baseline and white after three months, is, even to the naked eye, much larger than the difference between the other two sets of bars for gabapentin patients, isn't it?

A. It's very interesting that with placebo, the level appears to rise in contrast to the gabapentin, which appears to decrease.

Q. Do you think placebos increase 5-HIAA turnover, Professor Trimble?

A. No, but it's quite possible that over a period of three

months, there is an alteration of 5-HIAA in those patients on placebo for other reasons.

Q. Not because of any active agent at all, that may change, correct?

A. It may well go up for reasons that I don't know.

Q. And that is precisely the reason why it's so important to look at placebo-controlled data, isn't it?

A. There is placebo-controlled data here, that's correct.

MR. HOOPER: Just two more questions, your Honor. Slide 37, please.

(Discussion off the record.)

Q. Professor Trimble, do you recall what you told me about the relevance of randomized placebo-controlled data that specifically look at suicide attempts and ideation for 5,194 gabapentin patients versus 2,628 placebo patients when you sat for your deposition?

A. Yes.

Q. You told me then, Professor Trimble, that the placebo-controlled data are not relevant to the issue of general causation, correct?

A. That is correct.

Q. And in fact I asked you again. I said, "I want to give you another chance on that," and I reasked the question, and you restated that it was your opinion that the randomized placebo-controlled data for Neurontin were irrelevant to

general causation, correct?

A. It is correct in this case.

Q. And the FDA alert --

JUDGE SARIS: Wait, wait, wait. Why?

THE WITNESS: Your Honor, that statement I made is correct.

JUDGE SARIS: Well, why is it correct?

THE WITNESS: If I may explain.

JUDGE SARIS: That's why we're here.

THE WITNESS: I'm not doubting the importance of placebo-controlled investigations. And placebo-controlled investigations are the gold standard for looking at therapeutic effects, and they are generally designed to look at therapeutic outcome; in other words, in epilepsy, for example, a decrease in seizures. Placebo-controlled trials are not designed to look at adverse outcomes, although, of course, adverse outcomes are collected; and I do not know of any placebo-controlled trial that has specifically looked at suicide and suicidality as the prime outcome.

Now, the difficulty with these studies -- and this is where you have to have knowledge of neurology, epilepsy, as well as psychiatry -- the difficulty with Neurontin is that it was initially developed as an antiepileptic drug. And not all but a lot of the patients included in the analysis of the placebo-controlled trials were in epilepsy

studies.

Now, I'm not certain of the situation in the United States, but certainly in the United Kingdom, because of the concern of the adverse behavioral effects of GABAergic drugs, people incorporated into the placebo-controlled trials were ones who did not have a history of psychiatric disorder. So high-risk people for that which we are talking about, overdosing, suicide, suicidal ideation, were not included in many -- I'm not saying all -- but many of those placebo-controlled trials.

Now, when you look at who was included in those trials -- and these data are available in the information which has come from FDA, et cetera, recently -- the number of patient years in those trials for people with psychiatric disorders, as opposed to pain and epilepsy, the number of patient years was 21.

Now, if I'm being asked whether a study of 21 patient years is sufficient to give you a signal for an event, which I am told would require nearly 6,000 patient years of clinical data to accumulate, simply because of the frequency with which you get the side effect, I maintain in my deposition, and I maintain now, that the limited number of patients, specifically excluding in many cases high-risk patients for psychiatric disorders in the double-blind trials, will not give you information that you require on the

link between in this case Neurontin and these side effects, suicide, suicidal ideation, and the like.

JUDGE SARIS: Because of the population used?

THE WITNESS: Because the population studied largely exclude those at risk. And, as I have said, the number of patients in those studies that had predisposition psychiatric disorders was extremely small. It was less than three percent of all of the patients that Mr. Hooper has just put before me as the total number that were examined.

MR. HOOPER: Just a couple more questions, your Honor.

Q. Isn't it true, Professor Trimble, that the real reason you claimed RCT data was irrelevant at the time you report your deposition is that when you look at the 5,194 patients in total in gabapentin trials against 2,682 placebo-controlled, there are no suicides, no suicide attempts, no preparatory acts toward imminent suicidal behavior, and an identical tiny rate of suicidal ideation in that pool of RCT data?

A. Can I just --

JUDGE SARIS: RCT means?

MR. HOOPER: Randomized control trial, your Honor. I'm sorry.

JUSTICE FRIEDMAN: Are these the Pfizer trials?

MR. HOOPER: Yes, ma'am, they are?

A. Mr. Hooper, may I just clarify which document this comes from?

Q. It's the June, 2006 submission, Professor Trimble, and there is a copy of it, and you saw it at your deposition, and there is a copy of it at Tab H in your binder, Page 4, Table 2.

A. Yes, these were the data which were provided which included even a large number of trials where people only had a single tablet?

Q. In some, and in many others, they were longer. This is all of the randomized placebo-controlled clinical trials submitted to FDA.

A. But, again, your Honor, this rather supports what I was just saying; that a number of the trials which have been submitted were on people who had only received a single tablet. Now, I can't think that a suicidal act or ideation, and certainly the biological case that I am raising here, would occur after a single tablet.

JUDGE SARIS: So I understand that, you mean they only took it once?

THE WITNESS: Just one dose, you know, so these data are based upon trials which have included not only people who have been taking it for three or four weeks and measuring outcomes, but people who have taken a single dose, as I understand it.

JUDGE SARIS: And is this also a cohort that would not have high-risk psychiatric problems, do you know?

THE WITNESS: That would be my contention, as my last explanation to you, your Honor.

JUDGE SARIS: Is this disputed, by the way? Are these single doses?

MR. HOOPER: Some are, your Honor. I'd be happy to bring that up.

JUDGE SARIS: I just want to understand.

MR. HOOPER: Sure, sure.

JUDGE SARIS: And did you include in this people with psychiatric problems, or is it like the United Kingdom where they excluded those people?

MR. HOOPER: Patients with epilepsy, bipolar disorder, a wide range of underlying conditions that make them at extremely increased risk for suicide were included in these studies.

JUDGE SARIS: So these are epileptic people?

MR. HOOPER: Many are, and others have other primary indications, such as bipolar disorder, chronic pain states.

JUDGE SARIS: So this was a clinical trial for the test on epilepsy?

MR. HOOPER: These are all of -- this is on a body of 52 separate clinical trials for a range of different

patient populations, your Honor, so it's a large group of people.

JUSTICE FRIEDMAN: Was this the one with the 14,000 people? How many people were studied?

MR. HOOPER: Your Honor, let me be clear. This 5,194 represents the total number of Neurontin-exposed patients in some 52, I believe, approximately 50 separate clinical trials, separate studies conducted over years. The placebo would be the total number of patients which goes to placebo there.

JUSTICE FRIEDMAN: And this was the data that was submitted to the FDA before its issuance of the alert?

MR. HOOPER: Correct, your Honor, correct. And would you please put up --

JUSTICE FRIEDMAN: While you're looking for that, I just want to ask the professor. I'm going back. Did you identify in your report for this case any scientific methodology that you followed in reaching your conclusions other than the methodology in the medicolegal book that we looked at earlier this afternoon, and if so, what methodology did you identify?

THE WITNESS: Yes, thank you for the question, your Honor. As a neuroscientist, I have prepared a report based upon the methods that I use in all my research, and also when I write books or write learned articles. In other words, one

reads literature, incorporates that into the overall scheme of your understanding -- in my case, of how the brain works -- and then crystallizes all of that into a coherent model, if you like, as to explaining cause and effect, because cause and effect is always based on models. So as a neuroscientist, my method is peer-reviewed literature, literature searches; importantly, discussion with colleagues about the latest information, the latest data; and attending international conferences, going to meetings; and, of course, my own research. And my own research in this field -- namely, that of examining the effects of antiepileptic drugs on behavior -- goes back nearly 30 years. So I have a considerable mountain of information that I bring to preparing reports such as this.

Q. And, Professor Trimble, when I asked you almost verbatim the same question that Judge Friedman just asked you, you spoke of no mountains. Instead, you said you followed that Chapter 9 that we started with today, didn't you?

A. If you'd like to go back to Chapter 9, I make it quite clear that the most important -- you can read it, but it's in there -- the most important thing in examining causality, biological causality, is the empirical method. And the empirical method is a long-standing method of psychiatric or scientific inquiry, posing hypotheses and testing them. And it's in there clearly. The empirical method is what I imply

I have used.

MR. HOOPER: Professor Trimble, thank you very much. It's nice to see you again.

Judges, my time is up, and I will pass the witness.

JUDGE SARIS: But before I let you go, you've put up a graph, the last one up there, that I thought you'd ask about.

MR. HOOPER: I'd be happy to, your Honor.

JUDGE SARIS: The FDA statistic.

MR. HOOPER: Sure.

JUDGE SARIS: This is from the most recent FDA statistics the plaintiffs gave us last week, right?

MR. HOOPER: Indeed it is. Your Honor, it's Figure 4 from their statistical analysis and review.

JUDGE SARIS: Yes, well, obviously this is the key thing, the FDA, so maybe -- I don't know if, Dr. Trimble, you've ever seen that?

THE WITNESS: Your Honor, I've seen many -- these are called tree graphs, and which one exactly this is --

JUDGE SARIS: If you're not familiar with it, we won't take time.

MR. HOOPER: Oh, I am familiar with it and --

JUDGE SARIS: No, I know you are. The question is whether Dr. Trimble is.

THE WITNESS: I feel it's a question for others to

answer.

JUDGE SARIS: Okay, thank you.

MR. HOOPER: Thank you, your Honor.

JUDGE SARIS: Now, hold on. You have 30 minutes, right? We should probably have a break. We've been going for two hours, and for court reporter purposes and, frankly, for ours as well, why don't we just go off the record right now just for our scheduling.

(A recess was taken, 4:10 p.m.)

(Resumed, 4:25 p.m.)

JUDGE SARIS: So I'm assuming you all did the raw math. If everybody does an hour and then a half an hour, we will not finish tomorrow. Let's finish this witness and then talk about how we're going to schedule everything.

MR. FINKELSTEIN: Thank you, your Honor.

REDIRECT EXAMINATION BY MR. FINKELSTEIN:

Q. I want to start off, Professor Trimble, by clearing up some mischaracterizations, if I may. The defendant said something about the Hill criteria.

MR. FINKELSTEIN: Can we mark and I'll hand up to your Honors -- I'll offer it as an exhibit. One can be the original. And this is all I have.

(Plaintiff Exhibit 2 received in evidence.)

(Discussion off the record.)

Q. I just handed up to you, Professor, an article by Austin

Bradford Hill. Do you recognize that?

A. I do.

Q. And when Mr. Hooper asked you a question about your book, Chapter 9, and you responded about empirical evidence, what is empirical evidence?

A. Empirical is observation of scientific evidence.

JUDGE SARIS: No. Can I tell you what we were talking about upstairs?

MR. FINKELSTEIN: Sure.

JUDGE SARIS: I don't need to hear about Kant and Nietzsche or all of this stuff. I need to understand the science, okay? So they're great and I studied them. I want to understand what's happening here. So what's important here is for you to explain to us the scientific principles that govern what his basic opinion is and what it's based on, okay? Let's just jump to that. You have half an hour.

Q. Professor Trimble, why don't you tell her your scientific opinion and how you came to it.

A. Would it help if I just drew this quickly on something?

JUDGE SARIS: We need to be taught.

THE WITNESS: Your Honor, I will do my very best. Where would I draw it?

Q. Now, Professor Trimble, you rendered an opinion that Neurontin leads to suicidality. And before you actually do that, Professor Trimble, I just want to offer this book.

This book is what, Professor Trimble?

A. Oh, that is the last edition of my text on "Biological Psychiatry," which is a teaching book explaining neurotransmitters, neurons, neuroscience basically, and how that relates to psychiatric illness, from schizophrenia to panic disorder, but also including depression.

JUDGE SARIS: What medical schools use that book?

THE WITNESS: Oh, I really can't answer it. It sold very well, and I'm writing the third edition. I can only tell you it was a bit of a best seller at the time, but --

(Laughter.)

THE WITNESS: But what medical schools use it, I don't know.

JUDGE SARIS: Well, was it written more for people like me, or more for medical students, or more for doctors in the field?

THE WITNESS: It was really written for post-graduates who were interested in brain science and psychiatry and neurology, so postgraduate level.

JUDGE SARIS: It wasn't on the New York Times Best Seller List?

THE WITNESS: No.

JUDGE SARIS: All right, so really it was a professional book geared to --

THE WITNESS: That is correct, your Honor.

(Plaintiff Exhibit 1 received in evidence.)

Q. And contained within this book, do you describe the methods to evaluate how drugs affect brain chemistry?

A. The methods within that book are the methods that I've described, which has to do with how a scientist evaluates data and produces it, but it doesn't specifically outline a methodology because that's not what a book like that does.

Q. Well, did you describe how one would evaluate drugs' effect on brain chemistry in this book?

A. What is in there is how you make diagnoses and how you evaluate data, yes.

Q. And did you follow the methods of how you evaluate data that you outline in that book in your preparation of your report?

A. That's correct.

Q. Why don't you explain to the Court how Neurontin in fact implicates suicidality in humans.

A. It's a very simple statement that I'm going to make to show you. So Neurontin, we have peer-reviewed evidence in my report leads to an increase of this -- excuse my writing, but it's a little wobbly -- GABA within the central nervous system.

Q. Now, you describe peer-review evidence supports Neurontin increases GABA. Are there any objective tests that

support that? And describe for your Honors what an objective test --

JUDGE SARIS: Well, actually, this point was conceded, so we don't need to spend much more time on it. They agreed, it increases GABA within the central nervous system.

THE WITNESS: And the key studies are spectroscopy, which we've heard about, but there are other studies which support spectroscopy, that the increase in GABA in the human brain is physiologically active and increases inhibition in the brain. In other words, it's not simply that it's stuck in the cells. The GABA comes out of the cells and alters the physiology of the human brain.

JUSTICE FRIEDMAN: Professor, the defendants seem to be making some distinction between increases of GABA in the whole brain and increases in the raphe. I hope I pronounced that correctly. If you have a position on that distinction that is being made, it would be helpful if you articulate it in the course of your presentation.

THE WITNESS: I will do that immediately, your Honor.

MR. FINKELSTEIN: And can I just add one comment. Everything that's supported by peer-review literature and that which you've cited in your report, would you highlight. Not necessarily the literature. I know you don't have that,

but --

THE WITNESS: The increase in GABA, which is measured in part of the brain, the cortex, leads to a change of serotonin. And it is serotonin which is in, as you quite rightly said, the raphe nuclei. Okay, so it's the serotonin comes from the raphe nuclei, which are small nuclei well down underneath the cortex of the brain. The GABA increase occurs all over the brain, but it's the raphe that have to do with the serotonin side of the story. That was the serotonin side of the story.

So the small cells in the raphe nuclei down and deep in the brain release serotonin, but the increased GABA leads to a decrease of the serotonin. So that's quite straightforward. Here we've got A, Neurontin increasing GABA. Here we have B, increasing GABA, decreasing serotonin.

We know from biological psychiatry, it's one of the most secure findings in biological psychiatry, that if you decrease the turnover of serotonin in the human brain, you get changes of behavior which include mood disturbances, but most particularly suicide -- and there's a lot of work in my book described on this -- and, even more importantly, suicide by violent means, a violent suicide.

So this is C. So the straightforward, the logical contention is that A leads to B, B leads to C, and therefore

A leads directly to C. That is the summary of the case. And all of these steps are supported in the brain-based literature, the scientific neuroscience literature. That is the basis of the case.

May I explain further, or is that clear, your Honor?

MR. FINKELSTEIN: Well, it's Judge Friedman's question, so I'll move forward. Okay, as long as the Court is satisfied.

JUSTICE FRIEDMAN: Thank you.

Q. Professor Trimble, while you're still standing there, can you explain why the increase in the whole brain GABA, whether that is significant or not and why?

A. There has been a suggestion that -- and, by the way, only in this case, not from the papers that these data come from -- that somehow if you increase GABA in the central nervous system by a figure of 30 or 40 percent, it has no physiological effect, it has no effect on the behavior of the nerve cells. Not only does this seem highly improbable, highly implausible, but there are other studies in addition to the spectroscopy where you show the increased chemical that shows that the increase in GABA that you see following gabapentin administration leads to a slowing down, an inhibition of the nerve cells actually in the brain. And these data are EEG data. That's where you measure the brain

waves. And it's been done in volunteers. You give gabapentin to volunteers, and you can show it alters the brain waves.

And also there's another method, which I don't want to go into, but where you stimulate the brain very rapidly with magnetic pulses, and by doing that, you can see how quickly the neurons are working in the brain. And after single doses of gabapentin, you can show a slowing down of the neuronal traffic, the nerve traffic in the cortex.

So these increases in GABA are physiologically relevant and important. They're not merely a side observation. They are physiologically important.

JUDGE SARIS: Well, how do you explain the data that in the clinical trials of the Neurontin that was handed over to the FDA, the fact, if it's such a simple equation, why haven't there been more suicidal kinds of events?

THE WITNESS: Well, let me be very clear that not everybody that takes this particular drug has this particular effect.

JUDGE SARIS: Sure. They claim, though, it's 5,194 people, and they claim that there are only two even remotely suicidal ideation kinds of events.

THE WITNESS: Yes, because these events are relatively rare. If a drug caused more of those events, they would never get onto the market, if I can put it like that.

And so I hope I explained that this part of the story has an important endogenous component, a component of the people who you give the drug to. If you have somebody with very insecure serotonin metabolism -- in other words, somebody with a mood disorder --

JUDGE SARIS: Like bipolar or something like that.

THE WITNESS: Exactly, that's absolutely correct, your Honor. And I pointed out that less than 3 percent of those patients in those trials had bipolar disorder or some kind of psychiatric disorder, so you would not expect in a population of 3 percent of the 5,000 to pick up suicide events.

And the other thing, your Honor, is that in pharmacological/pharmaceutical research, rarer side effects you do not pick up until the drug goes out on general release. When it's not given to 5,000 people, many of whom have had restricted the actual predisposition, it goes out to, we've heard, millions of people. And that's when you begin to pick up signals, and it's upon those signals that companies have to act.

Q. And when you say rare event, if an event is one in 30,000, would you expect to see any event when there's only 5,000 studied?

A. You would never pick up an event of one in 30,000 in the clinical trials that drug companies do because the numbers

are simply too small.

Q. Is that called powering?

A. The power of the statistics is not sufficient.

Q. And you were asked by Mr. Hooper with respect to whether or not you were the only one who says Neurontin is GABAergic or GABAmimetic. What is GABAmimetic?

A. GABAmimetic I believe was the term that the FDA used in their most recent document.

Q. I've put it up here, the statistical review and evaluation. Can you please go to the page where -- in this, did they not classify the eleven drugs into three different pockets?

A. It is traditional to classify antiepileptic drugs into these pockets.

Q. And what were they? What were the pockets? Up on the board, why don't you describe them.

A. The first is sodium channel-blocking drugs. The second is GABAergic, and they use "GABAmimetic" to get around, I think, some of the problems that have been raised by uses of the term "GABAergic." And then it says here carbolic and hydrosignificance. It's another way of trying to control seizures.

Q. And the second drug listed there, gabapentin, is --

A. Gabapentin is viewed by the FDA, and by a lot of my colleagues still, as a GABAergic agent. Now, I'm talking

about in the epilepsy field, which is where I do a lot of my work.

Q. And the fact that it's GABAergic, you would expect to find the increase in the GABA spectroscopy and the activation on GABA?

A. That is correct.

Q. And do you know --

JUSTICE FRIEDMAN: Excuse me. Why are you making the point of noting that gabapentin is recognized as GABAergic in the epilepsy field?

THE WITNESS: Well, because there's been some suggestion in this legal case that somehow gabapentin does not increase GABA in the central nervous system; but, as I emphasized in my evidence, it was developed as an antiepileptic compound specifically with an idea that it would increase GABA, and it was heralded with great enthusiasm that it was GABAergic when this spectroscopy was studied. So the idea that it isn't GABAergic is simply not in the peer-reviewed literature. All of the Pfizer documents that I have read say it's GABAergic.

JUDGE SARIS: And where is the peer-reviewed study that says that the decrease in serotonin leads to suicide that is violent suicide?

THE WITNESS: Yes, your Honor, that is all in my report. It's not one peer-reviewed study. There are

dozens -- well, a good twenty studies.

JUDGE SARIS: That says it leads to suicide?

THE WITNESS: Suicidality, suicide acts, but most particularly, violent suicide.

JUSTICE FRIEDMAN: I'm sorry. Didn't you testify when the defendants were questioning you that there was not one study that purports to demonstrate that gabapentin causes suicide?

THE WITNESS: This is to do with the double-blind studies that I've already suggested are totally --

JUSTICE FRIEDMAN: Are you talking about random controlled studies?

THE WITNESS: Yes, yes.

JUSTICE FRIEDMAN: Are you distinguishing them from peer-reviewed literature or epidemiological studies?

THE WITNESS: The epidemiological studies, your Honor, are the FDA data, as far as I'm concerned. There are single case reports in the scientific literature about people taking overdoses with Neurontin. I mean, but -- but, your Honor, if you review the documents from the company, 5 percent is the percentage of depression noted as a side effect in not just the clinical trials, in the double-blind trials, but in other studies as well. A figure of 4 to 5 percent depression regularly is seen in the side effect profile of this drug.

Now, it's not --

JUSTICE FRIEDMAN: Can I just ask something about the Petroff and Kuzniecky studies? A great deal of time was spent on them in defendants' examination, and my understanding is that they were being focused on because they didn't show any acute side effects as a result of decrease in serotonin. Is that --

THE WITNESS: An increase in GABA.

JUSTICE FRIEDMAN: Increase in GABA, they didn't discuss decrease in serotonin?

THE WITNESS: No. I think the point that was being made -- sorry.

JUSTICE FRIEDMAN: What I want to ask about that is, are these the only two studies that discussed the side effects from increased GABA? Where do these studies fall in the universe of literature on side effects? I'd like to have some context.

THE WITNESS: Yes, these studies were not looking at side effects, but Mr. Hooper -- sorry. What happened was that when it was put to me, Mr. Hooper pointed out to me that some 20 percent of these -- one study was on volunteers, people like you and I. Another study was on people with seizure disorders. He pointed out to me there was about a 20 percent reporting of side effects acutely, which I think is sufficient to suggest to me that this is having a toxic

effect on the central nervous system; ataxia, loss of balance, drowsiness, somnolence, I think the figure he showed me was 20 percent, which seems to me to be quite high.

Q. And these studies are individuals who took it that day, and they do the spectroscopy shortly thereafter?

A. That was correct, although he also pointed out the longer-term study which shows after some weeks that gabapentin raises GABA levels in the central nervous system, but he also pointed out the side effects were still reported then.

Q. And there were only eleven people in that study, I believe?

A. I don't remember.

Q. It was a small number?

A. Yes. I think it was ten people.

Q. Ten people? And would it surprise you whether or not there's an adverse event of suicidality in an N of 10?

A. You would not expect.

JUSTICE FRIEDMAN: Are there other studies that discuss the side effects from an increase in GABA?

THE WITNESS: There certainly are.

JUSTICE FRIEDMAN: Have you identified them in your report?

THE WITNESS: Yes, the one I have mentioned in my report, your Honor, is a brain wave study. Now, an EEG, you

know, where you measure the brain waves, electrical brain waves, there was a study done on volunteers, people like you and I, given gabapentin; and they were given the drug, and the brain waves were measured, and their side effects were monitored. And not only did gabapentin alter the pattern of the brain waves in a direction showing inhibition, in keeping with this, but the amount of change of the brain waves was correlated with the reporting of the subjective side effects that people had. And these were volunteer studies, so people have looked at these effects in gabapentin.

Q. Did the FDA take all of in their most recent statistical review and they put together as a group the entire GABAergic class and evaluate the adverse events for them?

A. They did.

MR. FINKELSTEIN: And it's up on the screen, your Honors.

Q. You're looking at the sub just GABAergic class, and it's up on the screen, if you want to look at it. Can you tell us what significance, if any, that has with respect to the GABAergic subgroup of anticonvulsants causing suicidality?

A. Merely that the statistics showing the increase in suicidality, and at the bottom you have the overall value, which is -- these are FDA statistics. And if -- okay, there's no pointer. But the GABAergic agents clearly fall to the right of the line of one, which is like a center point

for the --

Q. And what does that mean that it falls to the right?

A. It means there's an increased chance with those agents, a significantly increased chance with those agents of having a suicide event.

Q. And that significant increased chance of having a suicide event is compared to placebos?

A. These data were, I believe, on placebo-controlled trials.

Q. Placebo-controlled trials?

A. Yes.

Q. So the evaluation of the GABAergic drugs showing an increased risk of suicidality compared to placebo in fact supports the position that you outlined in your paper, does it not?

A. The FDA data is a piece of the jigsaw which fits together with the biological evidence that I have brought forward in my paper.

Q. And have you ever seen any article that says Neurontin doesn't cause suicide?

A. No.

Q. Or doesn't lead to suicidality?

A. No.

Q. Has it been studied that you're aware of?

A. No.

Q. Just that there are no peer-reviewed articles out there whatsoever?

A. No, there are no peer-reviewed articles.

JUDGE SARIS: Let me ask you, Pfizer makes much of the fact that the FDA pooled the GABAergic drugs and that the different drugs have different chemistries, and that when you actually look at gabapentin, it's at the least risky side, for want of a better word. Would you agree with that, that the pooling is not scientifically reliable?

THE WITNESS: I'm not an epidemiologist, and I would really rather defer that to others.

Q. As part of the FDA study we're talking about, I put up a slide. If you can look at this slide and explain this slide and what that means and as a relationship to gabapentin, because did the FDA extract out the single-pill, as you described them, studies?

A. The interesting thing to me about this slide, this picture, it doesn't necessarily relate to these drugs here, all of which fall to the right of the central odds ratio of 1. All of these fall to the right.

Q. And falling to the right again means increased suicidality?

A. Increased risk of suicidality. Very interestingly, these two drugs, carbamazepine and Divalproex, which is called valproate acid, fall to the left; and, of course, it

is these two drugs which we know have some beneficial effects on mood.

Q. And did you outline that in your report as well?

A. I did.

Q. And were you surprised by the findings?

A. It vindicates again my distinguishing in my report these two drugs from the GABAergic agents.

Q. And to the right of the line, it indicates there's a generally increased risk to suicidality, correct?

A. And the overall risk shown down here, the finding as well is significant.

Q. In the overall?

A. Yes.

Q. I'd like to know, Professor Trimble, with respect to your methodology, did you consider temporality related to Neurontin's causative effect on suicidality?

A. By that, you mean that an effect follows a course?

Q. Yes.

A. The temporality is very clear that if you give a dose of Neurontin, you see an increase in GABA in the central nervous system reliably and reproducibly. So you give a drug, and you see the biological effect is temporality.

Q. And, by the way, didn't Pfizer hire you or retain you to evaluate the causative effect of gabapentin previously?

A. I did two reports for Pfizer quite some time ago on the

behavioral effects of Neurontin.

Q. And when you did those reports, they were in 1995 and 1996?

A. That is correct.

Q. Were you asked to consider the world of literature and everything related to the adverse effect profile of gabapentin, or were you asked a very specific question?

A. I was asked a specific question.

Q. And as part of that specific question, did you evaluate fifteen to twenty specific cases?

A. It was somewhat more than that, but I --

JUDGE SARIS: Why don't you tell us what you did for them.

THE WITNESS: They were concerned about psychosis, your Honor, in relationship to their drug. And I was asked, first of all, to examine a quite small number of cases who had had psychosis on gabapentin, and I was unable to document that there was a link to psychosis.

They then sent me a much larger database of some, oh, fifty or sixty patients. Actually, it was seventy patients.

Q. Before you move on to the second database, in the first report, did you advise them that there's a link between gabapentin and depression?

A. I made a point that one of the strongest associations

with antiepileptic drugs and behavior was to depression and not to psychosis.

Q. And is there a biological difference between psychosis and depression?

A. Yes, there is.

Q. So one can have a psychotic event and have nothing to do with depression from a biochemistry standpoint?

A. That's correct.

Q. And what did you do in your second report?

A. I analyzed more cases of psychosis, but they also included thirty-three cases of depression and twenty-one patients who had become aggressive. And I could not find a link with psychosis. I told them that two out of ten cases of depression I thought were possibly linked to the drug, 20 percent. And, interestingly, at that time, four out of nine cases that I could evaluate for hostility and aggression I suggested were possibly related to the drug. Sorry, four out of twenty-one, I do beg your pardon, four out of twenty-one. And five I thought were de novo, which was new cases of induced aggression and hostility after being given gabapentin.

I should make that clear once more. There were twenty-one cases of aggression. For twenty-one cases of aggression, I could analyze the data only from nine where I thought there was a link. So the others I didn't think there

was a link. But of those nine, there were five cases, which is five out of twenty-one of new cases of hostility and aggression.

Q. And the fact that it was a new case is significant for what reason?

A. Well, my warning was that psychosis may not be the problem, but that release of aggression and hostility may be a problem.

Q. And how is release of aggression and hostility related to suicidality?

A. Because of the decrease in serotonin and the increase of violent suicide.

Q. And the methods that you used when Pfizer retained you to do these evaluations, did you use the same methods that you applied in this case here?

A. Well, yes.

JUDGE SARIS: So do these results have any impact on whether or not this was an appropriate kind of drug to be using on people with bipolar or those kinds of cases that we have in these 700 cases?

THE WITNESS: Yes. Thank you, your Honor. That's of course a most important and relevant question, and my warning was that this, along with other antiepileptic drugs that affect GABA, should carry some kind of warning to doctors or patients that these behaviors may be seen with the

prescription of drugs in susceptible patients.

Now, at this time the drug was only used for epilepsy, and, to my knowledge, even to this day, the drug, certainly in the United Kingdom, is very limited in the prescription.

JUDGE SARIS: At this point was it being marketed for bipolar, do you know?

THE WITNESS: Not at all. I don't believe it's been marketed for bipolar disorder anywhere in the world at any time.

Q. I think you're using two difference definitions, marketed from a business standpoint, marketed from an approval standpoint. Can you explain that difference for her Honor?

A. I'm sorry, your Honor. A drug needs a license to be -- doctors look at what the drug is approved for by regulating authorities. What I should have said is, I do not believe that Neurontin has a license for use anywhere in the world in bipolar disorder; and at this time when I was doing those early reports, as far as I know, it only had the product approval for epilepsy.

Q. But the company may have marketed it for bipolar, but it may not have been approved for bipolar? That's the distinction, right?

A. I think there's a big difference between approval and

marketing.

Q. Would it have been appropriate for the company to market the drug gabapentin for bipolar treatment based on the information you provided to them in 1995 and 1996?

A. I believe it would have been a dangerous maneuver.

Q. And why is that?

A. Because there's a signal that it's a GABAergic agent that can lead to deleterious behavior, including depression. But I have to say, Mr. Finkelstein, a lot of the discussions have been about depression; whereas, the signals for hostility and aggression, which of course you don't find in DSM manuals or whatever, but this to me is just as important as depression, the release of hostile aggression in people with these antiepileptic and GABAergic compounds.

MR. FINKELSTEIN: That's all I have, your Honor.

JUDGE SARIS: All right. Well, thank you very much, sir.

JUSTICE FRIEDMAN: Thank you.

(Witness excused.)

JUDGE SARIS: So what should we -- I haven't even had a chance to talk to Judge Friedman yet, but the thought occurred to me, at the risk of turning everything around, it might be useful to do the 30 minutes first -- in other words, the positive presentation first, if you will, for both sides -- and then have the hour of cross afterwards.

MR. FINKELSTEIN: Sure.

MR. ROUHANDEH: I think that's fine, if your Honors prefer.

MR. FINKELSTEIN: Frankly, your Honor, the reason --

JUDGE SARIS: It just struck me, our frustration a little bit was it seemed -- we've had a chance to read the report. At least I haven't read the attachments ever. I mean, there are boxes of them. So that when you flip one up on the screen, it's going too fast for me. I mean, I have to read it and the blowout comes. It's harder to learn. So, I mean, I've got the basic -- we both have read the basic materials, but if you're going to teach us anything, it makes sense to do the 30-minute summary --

MR. FINKELSTEIN: Sure, we're fine. You had an off comment when we were suggesting this, and you said, well, just throw them on cross-examination. That's the only reason why we're following it. We're happy to put them on first.

JUDGE SARIS: It may have been one of my bad ideas. I'm just simply saying it doesn't work. So would that throw everything off for you? I think it makes some sense really.

MR. ROUHANDEH: Yes, I think we're fine with that, your Honor.

JUDGE SARIS: And if you want to reserve five

minutes of it for a redirect, you know, you get 30 minutes in total, and we'll do it that way. But even doing it that way, we're not going to be done tomorrow. We'll be here at 9:00, and then we'll have to figure out what to do if all of them go the full amount of time, okay? Because just spinning out the amount of time, it's not going to finish. Okay? Great.

JUSTICE FRIEDMAN: May I just say, it would be helpful tomorrow, if it's possible, to have copies of the entire documents that you're questioning on the screen from, not depositions necessarily but scientific studies and literature.

MR. ROUHANDEH: We'd be happy to do that.

JUSTICE FRIEDMAN: Thank you.

JUDGE SARIS: Thanks. See you tomorrow.

MR. FINKELSTEIN: Thank you.

MR. ROUHANDEH: Thank you.

JUDGE SARIS: And you might want to talk afterwards about what you want to do if we don't finish, all right?

(Adjourned, 5:00 p.m.)

C E R T I F I C A T E

UNITED STATES DISTRICT COURT)
DISTRICT OF MASSACHUSETTS) ss.
CITY OF BOSTON)

I, Lee A. Marzilli, Official Federal Court Reporter, do hereby certify that the foregoing transcript, Pages 1 through 106 inclusive, was recorded by me stenographically at the time and place aforesaid in Civil Action No. 04-10981-PBS, In Re: Neurontin Marketing and Sales Practices Litigation, and thereafter by me reduced to typewriting and is a true and accurate record of the proceedings.

In witness whereof I have hereunto set my hand this 5th day of July, 2008.

/s/ Lee A. Marzilli
_____
LEE A. MARZILLI, CRR
OFFICIAL FEDERAL COURT REPORTER